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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Reference

1 Luks AM, Swenson ER. COVID-19 lung injury and high-altitude pulmonary edema: a false equation with dangerous implications. *Ann Am Thorac Soc* 2020;17:918–921.

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

indications for invasive mechanical ventilation do not progress to ARDS (9) argues against the notion that VILI is an inevitable outcome of mechanical ventilation under all circumstances, including COVID-19. Thus, although VILI has long been a clinical concern, the problem is not initiation of mechanical ventilation *per se* but rather initiation of inappropriate mechanical ventilation strategies, including an overly high tidal volume or distending pressure.

Although we agree with Dr. Kyle-Sidell about the importance of scientific debate, our ultimate concern with the author's letter and statements in other forums is that these and other claims about COVID-19 pathophysiology, such as the predominance of endothelial over epithelial injury, lack supporting evidence and are contradicted by the published physiologic, histopathologic, and radiographic evidence. In a time of high patient volumes and stress, there arises a risk that clinicians will latch onto such claims and abandon the approach to ARDS care that has been developed over many years of well-designed, well-controlled randomized clinical trials, which have yielded impressive improvements in mortality and other clinical outcomes. When faced with new diseases and clinical challenges, we should recognize that novel observations and hypotheses are important for advancing care. We must, however, keep the focus on conducting well-designed studies of these ideas so that we can come out on the other end of the pandemic with a solid sense of what does and does not work. Action based simply on conjecture and unsubstantiated claims will leave us with more uncertainty and may increase the risk of patient harm.

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

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References

1 Luks AM, Swenson ER. COVID-19 lung injury and high-altitude pulmonary edema: a false equation with dangerous implications. *Ann Am Thorac Soc* 2020;17:918–921.
2 Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, *et al*. Covid-19 in critically ill patients in the Seattle region: case series. *N Engl J Med* 2020;382:2012–2022.
3 Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, *et al*. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. *Am J Respir Crit Care Med* 2020;201:1560–1564.
4 Dolhnikoff M, Duarte-Neto AN, de Almeida Monteiro RA, Ferraz da Silva LF, Pierre de Oliveira E, Nascimento Saldiva PH, *et al*. Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19. *J Thromb Haemost* [online ahead of print] 15 Apr 2020; DOI: 10.1111/jth.14844.
5 Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, *et al*. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. *Histopathology* [online ahead of print] 4 May 2020; DOI: 10.1111/his.14134.
6 Tomashefski JF Jr, Davies P, Boggis C, Greene R, Zapol WM, Reid LM. The pulmonary vascular lesions of the adult respiratory distress syndrome. *Am J Pathol* 1983;112:112–126.
7 Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;201:1299–1300.
8 Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, *et al*.; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368:2159–2168.
9 Tejerina E, Pelosi P, Muriel A, Peñuelas O, Sutherasan Y, Frutos-Vivar F, *et al*.; for VENTILA group. Association between ventilatory settings and development of acute respiratory distress syndrome in mechanically ventilated patients due to brain injury. *J Crit Care* 2017;38:341–345.

Medical Thoracoscopy for Pleural Infection: Are We There Yet?

To the Editor:

We read, with keen interest, the randomized clinical trial of intrapleural fibrinolytic therapy versus early medical thoracoscopy (MT) for the treatment of pleural infection, which was published in a recent issue of *AnnalsATS* (1). We congratulate the authors for conducting a randomized study addressing an important clinical question. The authors have concluded that early medical thoracoscopy may have a role in the management of complicated pleural effusion and empyema, leading to a reduced hospital stay. However, some critical points regarding the reported results need careful consideration and further discussion.

The primary outcome chosen for the trial was the duration of hospital stay. This outcome measure is not ideal for a clinical question concerning the use of medical thoracoscopy. Other parameters, such as radiologic resolution or referral/need for surgery, would have been more meaningful for assessing the benefit of the intervention proposed (2, 3). Even though authors have used the duration of hospital stay as the primary outcome measure, there is no mention of discharge criteria, which should have been objectivized to maintain uniformity. In the inclusion criteria, it is mentioned that patients with not completely drained empyema were enrolled. Authors have not mentioned how long they waited for empyema to drain before enrollment. This time duration is vital because a delay in the intervention may be associated with the failure of the intervention. It is also not clear why the authors chose to put a small-size intercostal tube in all patients before randomization. In patients randomized to the MT arm, the initial tube placement could have