(1). In this letter, the authors describe 16 patients with coronavirus disease (COVID-19) who have a mean respiratory system compliance of 50.2 ± 14.3 ml/cm H_2O and marked shunt physiology. The authors suggest that these patients are representative of the primary pattern of physiologic derangements among their patients and those of colleagues with whom they've conferred. They discourage the use of prone positioning when compliance is "relatively high," similar to their recommendations in a recent article in which they additionally support ventilation with V_T up to 9 ml/kg in select patients with COVID-19 and relatively preserved compliance (2). We appreciate the authors' clinical observations and their expertise; however, we have several concerns with these two recommendations, which diverge from the best established evidence for acute respiratory distress syndrome (ARDS).

First, the authors' reported cohort is small and heterogeneous, in keeping with the well-established heterogeneity of ARDS. Many of their patients have similar compliance to those enrolled in clinical trials for ARDS therapies (3). For reference, patients enrolled in the PROSEVA (Prone Positioning in Severe ARDS) trial had a mean respiratory system compliance of 35 ml/cm H_2O (SD, 15) at the time of enrollment (3). Interestingly, a recent report of patients with COVID-19 from Seattle, Washington, described median respiratory system compliance of 29 ml/cm H_2O (interquartile range, 25–36) (4). That is to say, 75% of the patients in the Seattle cohort had lung compliance of 36 ml/cm H_2O or less. The discrepancy between the compliance measurements in the cohorts from Gattinoni and colleagues and Seattle highlights the difficulty in interpreting observations of small cohorts in a disease with well-established marked heterogeneity such as ARDS (5).

Second, respiratory system compliance was not used to determine eligibility for prone positioning in past trials. The PROSEVA trial enrolled severely hypoxemic patients, meeting the Berlin criteria for ARDS, who failed to stabilize early in the course of management (3). Though the authors may not support prone ventilation in patients with "relatively high compliance," exclusion of patients by these criteria would be inconsistent with existing evidence. Also, the effects of prone position on gas exchange are not limited to the shunt in fully atelectatic regions but instead include changes in edematous regions. Discouraging prone position based on a perception of limited recruitability risks foregoing a therapy with mortality benefit (3).

Finally, progression to a classic ARDS with dense posterior consolidation and elevated critical opening pressures (recruitability) is well described after mechanical ventilation, even in patients with initially preserved mechanics and without established lung injury (6). Patients with COVID-19–associated respiratory failure have multifocal pneumonia even in milder stages, and these regions are expected to have different elastic properties than unaffected tissue, causing regional stress and strain concentrations with potential to progress to severe ARDS (2, 4). Lung-protective strategies, including low V_T and prone positioning, exist to prevent this progression of lung injury.

We fully agree with the authors' final sentiment that patience and gentle ventilation are the best therapies for COVID-19 with associated ARDS. Furthermore, the rapid search for new insights into COVID-19 is appropriate and commendable. However, adopting the paradigm that COVID-19 is inconsistent with ARDS, with resulting specific treatment recommendations, risks discouraging compliance with our best evidence-based standards of care. Evidence from randomized controlled trials suggests that prone positioning and low V_T ventilation are the precise strategies for gentle ventilation that patients with ARDS, "typical" or not, should receive. ■

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COVID-19 Phenotypes and Potential Harm of Conventional Treatments: How to Prove the Hypothesis

To the Editor:

On the basis of recent correspondence (1) and an expert editorial (2), two phenotypes of severe coronavirus disease (COVID-19) pneumonia have been proposed: *"Type L, characterized by Low elastance (i.e., high compliance), Low ventilation to perfusion ratio, Low lung weight and Low recruitability and Type H, characterized by High elastance, High right-to-left shunt, High lung weight and High recruitability"* (2).

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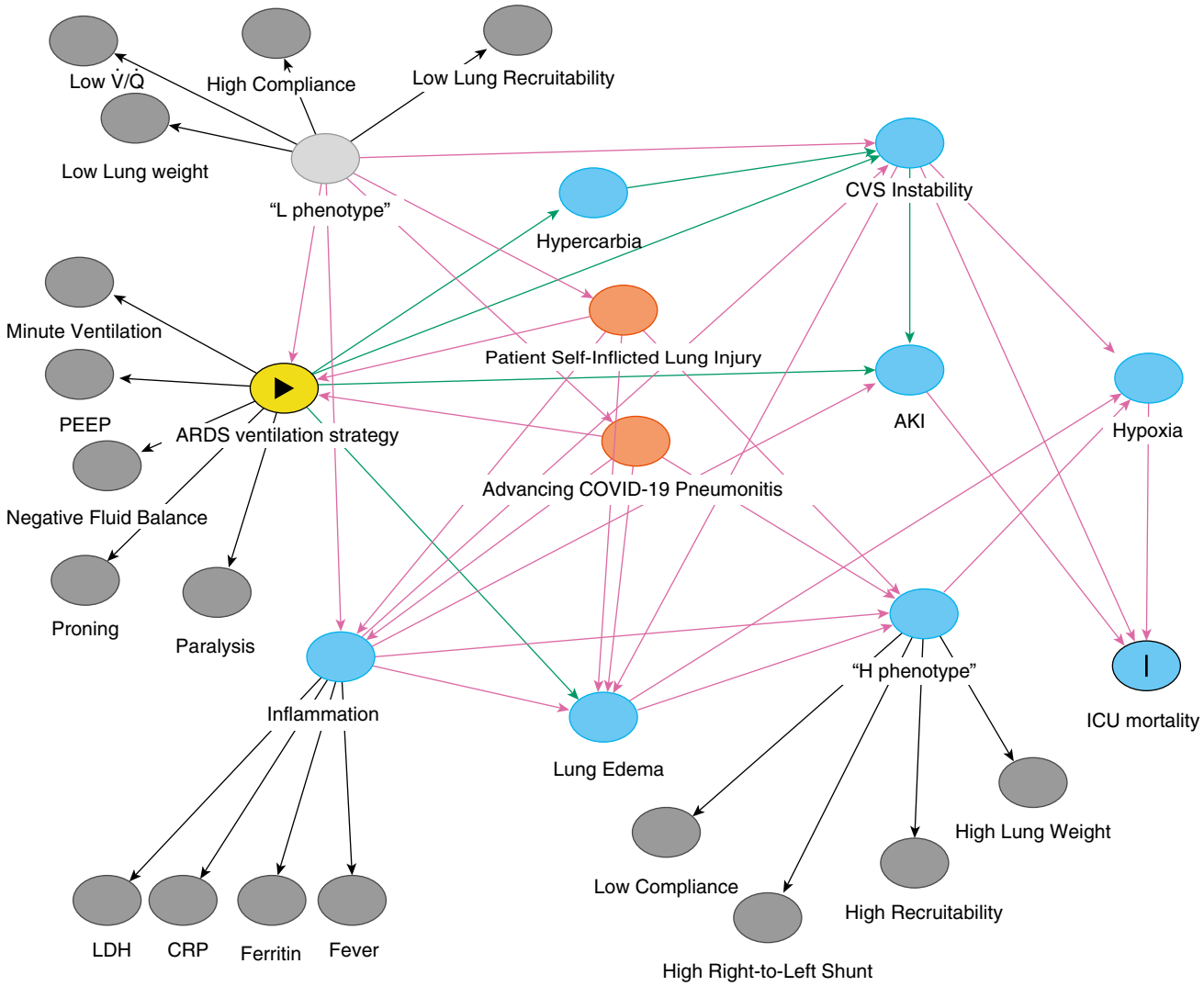

Figure 1. Proposed directed acyclic graph. Arrows represent proposed causal pathways. The solid triangle indicates exposure and the vertical line indicates outcome. AKI = acute kidney injury; ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; CRP = C-reactive protein; CVS = cardiovascular system; H = high elastance, high right-to-left shunt, high lung weight, and high recruitability; L = low elastance, low V̇/Q̇, low lung weight, and low recruitability; LDH = lactic-acid dehydrogenase; PEEP = positive end-expiratory pressure.

Features of the L phenotype are not typical of acute respiratory distress syndrome (ARDS) as defined by the Berlin criteria. Importantly, the authors suggest that recommended treatment strategies for severe COVID-19 pneumonia based on ARDS management (3) may lead to disease progression and excess harm (1, 2). The authors provide anecdotal evidence for their observations based on their combined experience of treating several hundred severe COVID-19 cases. As outlined by Singer and colleagues (4), we need a rational approach. Considering the potential importance for modifying the management of these patients and the growing volume of data available from China and Italy, quantitative data are needed to test this hypothesis. Balancing the trade-off between "learning" and "doing" in this pandemic is crucial (5). Large randomized controlled trials are not yet available, and observational data remain at high risk of bias. A number of predictive models have been described with severe methodological flaws (6). The appropriate use of emerging observational data requires collaborative input to improve understanding of treatment effects and complement the results of ongoing randomized controlled studies.

The wealth of data generated by critically ill patients and the complexity of covariate interactions make it challenging to use traditional statistical modeling to establish causal relationships. We aim to determine the causal pathway between the use of an ARDS management strategy for L-phenotype patients and subsequent harm using a directed acyclic graph (DAG) (Figure 1). The DAG achieves two things. First, we can construct a complex system of interacting baseline, clinical, and disease features, allowing explicit statement of prior knowledge before any data analysis. Second, we can use the DAG to determine a minimal adjustment set of variables to reliably estimate the direct effect of our exposure (ARDS ventilation strategy in COVID-19 L-phenotype patients) and outcome (ICU mortality).

The DAG was developed on the basis of the information in the expert editorial outlining the two phenotypes. In doing so, we have transformed the initial hypothetical construct into a testable

mechanistic structure. Arrows represent proposed causal pathways, such as the link between a high positive end-expiratory pressure strategy of standard ARDS management and worsening edema and cardiovascular instability. Combined, these paths can be used to elucidate the appropriate adjustment set of variables. In this case, one adjustment set included cardiovascular instability, hypoxia, and acute kidney injury, all of which are readily measurable among intensive-care patients receiving treatment for COVID-19.

This approach has a number of limitations, including the fact that the evidence underpinning the structure is currently anecdotal. Without high-quality, unbiased evidence, it will be challenging to determine the true direct effect because of unmeasured confounders. Highlighting different phenotypes and different responses to treatment is a welcome approach that echoes the thoughts of some intensivists treating patients with COVID-19 and, if supported through the appropriate use of data, has the potential to reduce harm to future patients. The DAG allows easy inclusion of increasing knowledge as new findings emerge and provides an objective analytical framework to facilitate ongoing discussion. We welcome comments and encourage readers to examine the structure themselves by running the code (code freely available on request). We would also be interested to know the calculated effects if anyone wishes to test the hypothesis with appropriately collected data. ■

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Severe Hypoxemia in Early COVID-19 Pneumonia

To the Editor:

Luciano Gattinoni is widely acknowledged and respected for his work on acute respiratory distress syndrome, and this time he has suggested a very interesting concept describing the pathophysiology of the atypical presentation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–induced respiratory failure (1). Based on detailed observation of several cases, the hypothesis of dividing the time-related disease spectrum within two primary "phenotypes," type L and type H, looks logical and might be helpful in the management of patients with coronavirus disease (COVID-19). The suggested cause of hypoxemia in type L is the loss of regulation of perfusion and loss of hypoxic vasoconstriction. Hypoxemia, leading to increased minute ventilation, primarily by increasing the V_T (up to 15–20 ml/kg), is associated with a more negative intrathoracic inspiratory pressure, and the magnitude of this pressure swing is projected as a factor that may determine the transition from the type L to the type H phenotype. However, the authors did not give an explanation for loss of regulation of perfusion and loss of hypoxic pulmonary vasoconstriction.

We believe that diffuse pulmonary microvascular thrombosis is the cause of hypoxemia in early pneumonia by SARS-CoV-2. The histologic and immunohistochemistry studies suggest that in severe COVID-19 infection, a catastrophic, complement-mediated thrombotic microvascular injury occurs, with sustained activation of the actin pathway and lectin pathway cascades (2), leading to the recommendation of the use of early anticoagulation with low-molecular-weight heparin (3).

We agree with the authors that to reverse hypoxemia, oxygenation by high-flow nasal cannula may be tried in patients with type L. However, we have reservations on the "early intubation and the use of PEEP [positive end-expiratory pressure] to prevent the transition to type H," as the authors themselves have suggested that "the lung conditions are too good." Effective oxygenation using high-flow nasal cannula/extracorporeal membrane oxygenation in type L should prevent pleural pressure swings and self-inflicted lung injury, leading to transition to type H.

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