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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Additionally, some degree of "permissive hypoxemia" (4) may also be accepted in patients with type L to avoid ergotrauma, caused during ventilating the compliant lungs.

However, other patients, who worsen to type H because of cytokine storm, as the authors have suggested, should be treated as severe acute respiratory distress syndrome, including higher positive end-expiratory pressure, if compatible with hemodynamics, prone positioning, and extracorporeal support. ■

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COVID-19–related Acute Respiratory Distress Syndrome: Not So Atypical

To the Editor:

Patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus frequently develop coronavirus disease (COVID-19)–related acute respiratory distress syndrome (ARDS). It has been advocated that ARDS related to COVID-19 is not "typical" ARDS (1) because patients have a better compliance of the respiratory system (Crs) that is discrepant to the amount of shunt. Later, it was specified that this relates specifically to "L"-type ARDS with a low elastance, low lung weight, and low $\dot{V}/\dot{Q}$ (2).

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Treatment recommendations that have been based on conceptional physiological models resulting from these observations go against long-standing evidence-based interventions such as low V_T ventilation and prone positioning (1, 2).

ARDS was first described over 50 years ago as a syndrome that presents with "acute onset of tachypnea, hypoxemia, and loss of compliance after a variety of stimuli; the syndrome did not respond to usual and ordinary methods of respiratory therapy." This description is strikingly similar to the common presentation of patients with severe COVID-19 pneumonia. The mean Crs of intubated patients with COVID-19 ranged between 30 and 50 ml/cm H_2O in two recent series (1, 3). These values are actually comparable with those reported in LUNG-SAFE, the largest observational cohort study to date (4). Though patients with non–COVID-19–related ARDS do frequently not show signs of diffuse alveolar damage (DAD) on autopsy (5), the available autopsy reports of patients who died from COVID-19 show DAD even in patients who never received mechanical ventilation (6). The available data indicate that severe COVID-19 pneumonia is similar to the original description of the syndrome and fits within the current consensus definition.

In recent years, the pulmonary critical care community has come to realize that ARDS can be split into subphenotypes (Figure 1) that might respond differently to interventions (7). Heterogeneity can be observed in *1*) the etiology of lung injury, *2*) physiological changes, *3*) morphology of affected lung parenchyma, and *4*) biological response. Based on *post hoc* analyses of randomized clinical trials, patients with systemic hyperinflammation might respond differently to higher end-expiratory pressure, restrictive fluid management, or immunomodulation with simvastatin treatment, whereas patients with a nonfocal lung morphology benefit more from recruitment than prone positioning (8, 9). However, no one is advocating for implementing these personalized approaches into clinical practice before they are validated in prospective clinical trials, despite a much stronger basis of evidence than is currently provided for COVID-19–related ARDS phenotypes.

Etiology is generally a minor determinant of the pathophysiological presentation of ARDS, meaning that many patients with a similar "hit" show different biological, physiological, and morphological patterns. COVID-19–related ARDS is an etiological subphenotype of ARDS with a particular set of characteristics: frequent DAD, (possibly) a higher than expected Crs, low Pa_{O_2}/FI_{O_2} values, frequent nonfocal morphology, and some suggestions of profound systemic inflammation (Figure 1). But are patients with COVID-19–related ARDS inherently different from "typical ARDS"? With appreciation of the heterogeneity within ARDS, we have come to realize that there is no "typical ARDS."

Despite the described heterogeneity that is inherent to the syndromic definition of ARDS, low V_T ventilation was found to decrease mortality in an unselected population, and prone positioning was effective in patients with persistent hypoxemia. Yet, these interventions are the ones that are now challenged for the supportive treatment of COVID-19–related ARDS (2). Does subphenotyping of COVID-19–related ARDS require a different level of evidence before we adjust clinical practice? Or were we too strict in implementing subphenotype-based interventions in the pre–COVID-19 era? I would argue that we should maintain the highest standard to adjust our clinical practice and resist the