

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. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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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 (Cr<sub>s</sub>) 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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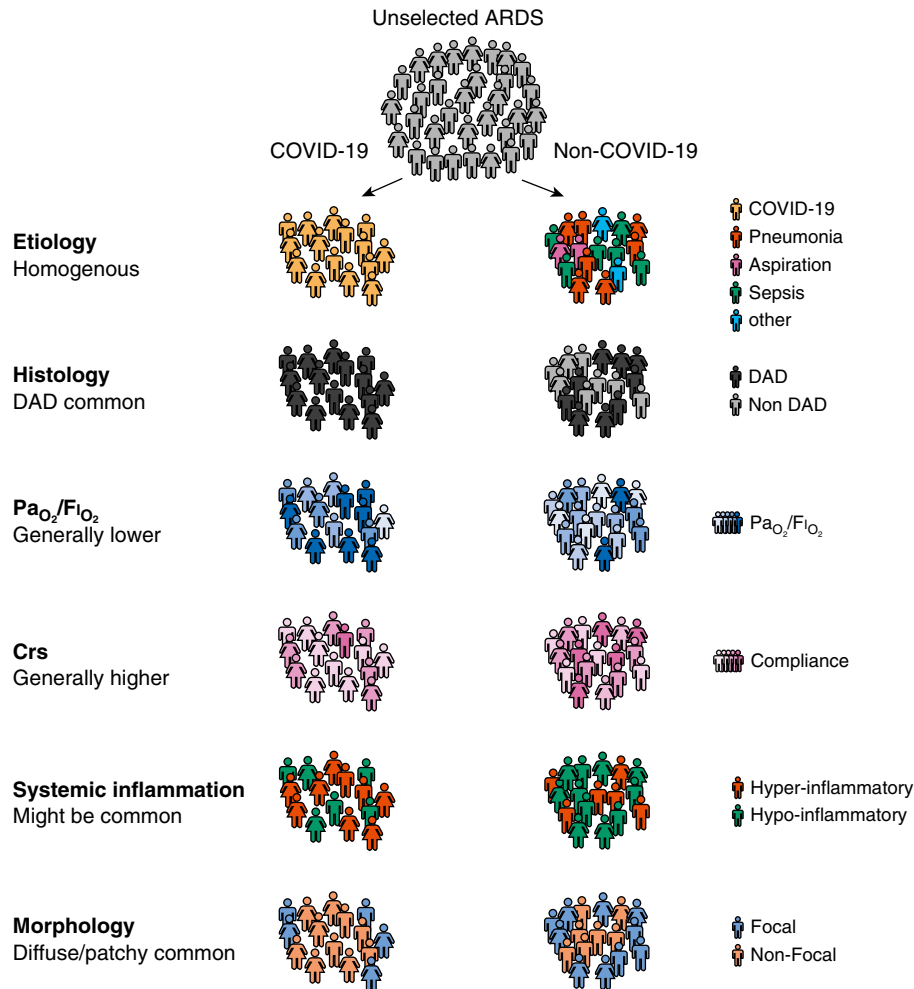
Treatment recommendations that have been based on conceptual physiological models resulting from these observations go against long-standing evidence-based interventions such as low V<sub>T</sub> ventilation and prone positioning (1, 2).

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 Cr<sub>s</sub> of intubated patients with COVID-19 ranged between 30 and 50 ml/cm H<sub>2</sub>O 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 Cr<sub>s</sub>, low Pa<sub>O<sub>2</sub></sub>/F<sub>I</sub>O<sub>2</sub> 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<sub>T</sub> 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



**Figure 1.** Subphenotypes of ARDS, stratified for the etiological subphenotype of COVID-19-related ARDS. ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease; Crs = compliance of the respiratory system; DAD = diffuse alveolar damage.

temptation to jump to conclusions and provide alternative treatments that might harm our patients. ■

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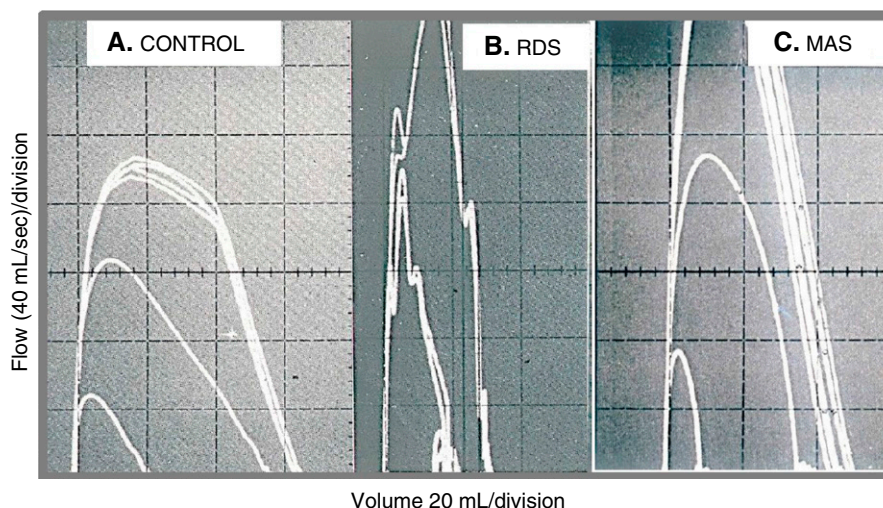
## Lung Mechanics in COVID-19 Resemble Respiratory Distress Syndrome, Not Acute Respiratory Distress Syndrome: Could Surfactant Be a Treatment?

To the Editor:

In a recent article in the *Journal*, Gattinoni and colleagues (1) reported that patients with coronavirus disease (COVID-19) fulfilling the Berlin criteria of acute respiratory distress syndrome (ARDS) presented an atypical form of the syndrome characterized by the “dissociation between their relatively well-preserved lung mechanics and the severity of hypoxemia” that is in sharp contrast with what is expected in severe ARDS. We believe that these findings are actually similar to what we have seen in prematurely born infants with severe respiratory distress syndrome (RDS) caused by surfactant deficiency.

We reviewed data from pulmonary function testing we had performed at the Children’s Hospital of Pittsburgh in neonates during the first week of life as part of an institutional review board–approved study of the natural course of respiratory failure in the neonatal period (2). Twelve prematurely born neonates who were mechanically ventilated because of respiratory distress syndrome (RDS group) were compared with 13 term infants with ARDS due to meconium aspiration syndrome (MAS group) requiring extracorporeal membrane oxygenation. Ten term newborns without lung disease, who had been briefly intubated for procedures under anesthesia, served as controls. The testing was done under sedation or general anesthesia with or without muscle relaxants.

The lung function was evaluated with the deflation flow–volume curve technique that has been described in detail elsewhere (3). In brief, volume history was established by inflating the lungs to TLC with an anesthesia bag system, using a standard inflating pressure of +40 cm H<sub>2</sub>O. The lungs were then rapidly deflated by opening the endotracheal tube to negative pressure reservoir via a three-way slide valve generating a standard pressure of –40 cm H<sub>2</sub>O for up to 3 seconds. Pressures of +30 cm H<sub>2</sub>O and –30 cm H<sub>2</sub>O were used for all neonates weighing <1,000 g. The lungs were immediately reinflated to TLC after the deflation. The produced airflow and integrated volume signals were plotted as a flow–volume curve (Figure 1). The procedure was repeated until three superimposed curves were obtained. The following indices



**Figure 1.** Deflation flow–volume curves (DFVCs) in intubated infants. (A) Term newborn without lung disease. The outer curves are superimposed DFVCs obtained with inflating pressure of +40 cm H<sub>2</sub>O and deflating pressure of –40 cm H<sub>2</sub>O; the middle curve is a passive flow–volume curve after the lungs were inflated with a pressure of +40 cm H<sub>2</sub>O; the small inner curve is a passive flow–volume curve from a standard pressure of +10 cm H<sub>2</sub>O and is used to calculate respiratory system compliance and resistance. (B and C) DFVCs from newborns with RDS and MAS. Note the tall and narrow configuration of the curves that illustrate the very high airway conductance seen in both conditions. MAS = meconium aspiration syndrome; RDS = respiratory distress syndrome.

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were calculated: FVC, maximum expiratory flow rate at 25% of the FVC (measured from the residual volume) (MEF<sub>25</sub>), and the ratio MEF<sub>25</sub>/FVC. Respiratory system compliance (C<sub>rs</sub>) was calculated from partial flow–volume curves produced by a modification of the technique described by LeSouef and colleagues (4) Specifically, the lungs were inflated to TLC and