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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_2O. 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_2O for up to 3 seconds. Pressures of +30 cm H_2O and −30 cm H_2O 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 were calculated: FVC, maximum expiratory flow rate at 25% of the FVC (measured from the residual volume) (MEF_{25}), and the ratio MEF_{25}/FVC. Respiratory system compliance (Crs) 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

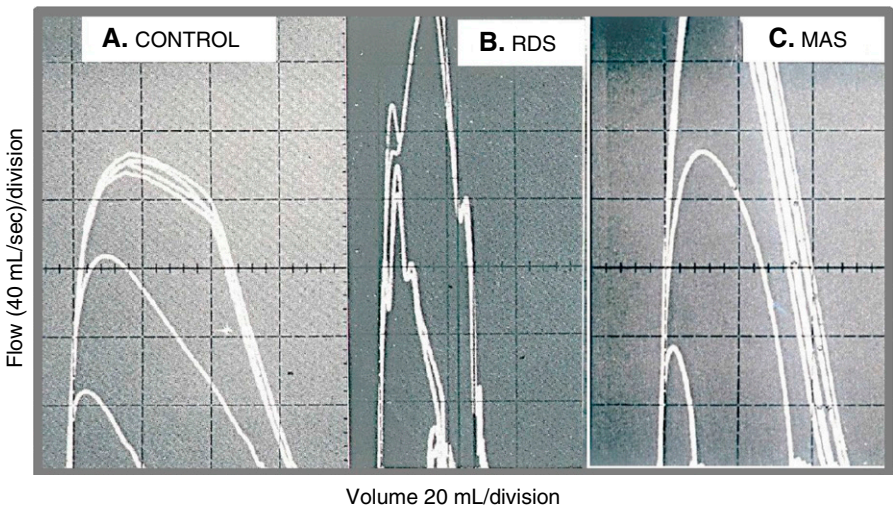

Figure 1. Deflation flow–volume curves (DFVCs) in intubated infants. (*A*) Term newborn without lung disease. The outer curves are superimposed DFVCs obtained with inflating pressure of +40 cm H_2O and deflating pressure of −40 cm H_2O; the middle curve is a passive flow–volume curve after the lungs were inflated with a pressure of +40 cm H_2O; the small inner curve is a passive flow–volume curve from a standard pressure of +10 cm H_2O 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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Table 1. Demographic Data and Indices of Lung Mechanics and Function

	MAS (*n* = 13)	RDS (*n* = 12)	Control (*n* = 10)
Postconceptional age, wk	39.5 ± 1.9	29.0 ± 2.7*	39.9 ± 0.8
Postnatal age, d	3.9 ± 2.0	4.0 ± 1.7*	2.7 ± 2.0
Weight, g	3,280 ± 397	1,256 ± 511*	3,174 ± 390
FVC/kg, ml/kg	19.7 ± 10.6†	39.1 ± 12.3	41.1 ± 7.3
MEF_{25}, ml/s/kg	37.9 ± 15.3	67.1 ± 40.4*	43.3 ± 16.0
MEF_{25}/FVC	2.2 ± 0.8†	1.9 ± 1.4	1.1 ± 0.4
Crs, ml/cm H_2O/kg	0.6 ± 0.5†	1.6 ± 0.4	1.7 ± 0.6

Definition of abbreviations: Crs = respiratory system compliance; MAS = meconium aspiration syndrome; MEF_{25} = maximum expiratory flow rate at 25% of the FVC (measured from the residual volume); RDS = respiratory distress syndrome.
*$P < 0.05$ compared with MAS and with control.
†$P < 0.001$ compared with RDS and with control.

then passively deflated from a standard pressure of 10 cm H_2O. All values were adjusted for body weight and are presented as mean ± SD. Comparisons between the groups were made with one-way ANOVA and the Student-Newman-Keuls test. A P value less than 0.05 was considered statistically significant.

The demographic information and the results of the pulmonary function testing for all patients are presented in Table 1. The FVC/kg and the MEF_{25}/kg as well as the Crs/kg were significantly decreased in the ARDS (MAS) group. In contrast, the lung volume and the Crs were near normal in RDS. The ratio MEF_{25}/FVC was significantly elevated in both the RDS and MAS groups, suggesting abnormally high upstream conductance (5). There were no adverse effects during the testing in any patient studied with the deflation flow–volume curve technique.

Our findings suggest that despite similarities in clinical and often radiographic manifestation, the lung mechanics are very different between RDS and ARDS. Specifically, in RDS, the lung volume and the Crs (adjusted for body weight) are near normal, but they are severely decreased in MAS. Both conditions show very high airway conductance (reflected by the elevated MEF_{25}/FVC) probably due to lack of surfactant. In RDS, the surfactant is normally absent because its production only starts at around 28 weeks of gestation. Because the lung volume and respiratory system compliance are near normal (for gestational age), prematurely born infants can be successfully managed with supplemental oxygen and noninvasive continuous positive airway pressure even without exogenous surfactant (6). In contrast, in MAS, the surfactant is present but inactivated owing to meconium-induced inflammation, and its production is impaired because of alveolar damage (specifically of the surfactant-producing type II pneumocytes) (7).

Observations of patients presenting in the emergency room with severe hypoxemia but preserved lung mechanics have been reported even in the lay press (8). It has been suggested that there are different phenotypes of COVID-19 that will probably require different treatments (9). We believe that the presumed phenotypes may be in fact different stages of the same continuum, that starts with a surfactant-deficient RDS-type picture that causes severe hypoxemia because of extensive alveolar collapse. In that stage, adult patients respond to oxygen and noninvasive positive airway pressure in a similar way to the premature infants. Mechanical ventilation in that stage may be detrimental (especially when instituted by untrained personnel in the emergency room). Because the virus may affect other organs beyond the lungs, the patients may progress to full-blown ARDS that can become refractory both to oxygen and to invasive mechanical ventilation.

Whether early administration of exogenous surfactant could alter the course and severity of COVID-19 is not known. Trials of exogenous surfactant in typical ARDS have not been successful in the past (10), often because the intervention took place when the lungs had already suffered irreparable damage. Because children (especially newborns) are not just "small adults," it would be prudent to verify our findings in adult patients. Then a randomized controlled trial should start with the surfactant given as early in the course of the disease as possible, and not as a rescue. Several practical aspects such as dose, frequency, and mode of administration need to be determined. It is a complicated path but one worth investigating. ■

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

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Mechanics of Breathing and Gas Exchange in Mechanically Ventilated Patients with COVID-19–associated Respiratory Failure

To the Editor:

The acute lung insult resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has multifarious clinical presentations ranging from limited mild respiratory symptoms to a potentially fatal multifocal pneumonia/acute respiratory distress syndrome (ARDS) requiring weeks of mechanical ventilation. Whether these clinical presentations represent different levels of severity of the same "disease" or result from profoundly different pathophysiological mechanisms (virus invasion vs. inflammatory response of the host) remains an unanswered question. Three case series very recently published in the *Journal* (1–3) have reported conflicting data on the mechanical properties of the respiratory system and the gas-exchange profile observed in intubated patients presenting with SARS-CoV-2–induced respiratory failure. We have reanalyzed the data presented in these cases series (1–3) in an attempt to reconcile these discrepant observations and revisit some of the conclusions and clinical implications of these studies.

1. Do mechanically ventilated patients with COVID-19 pneumonia have well-preserved or deteriorated lung mechanics?

Gattinoni and colleagues (1) have reported in a cohort of 16 patients with a shunt fraction of ~0.5, values of compliance of the respiratory system (Crs) averaging 50.2 ± 14.3 ml/cm H_2O (1), that is, ~60% from normal. Based on these observations, the authors concluded that a relatively preserved compliance in patients with coronavirus disease (COVID-19) pneumonia would make "high" positive end-expiratory pressure (PEEP) ineffective, and thus unnecessarily dangerous, and make prone position worthless because of a low benefit/resource ratio. However, Crs values in this study were exceptionally variable, ranging from 20 to 90 ml/cm H_2O. In other words, a significant reduction in Crs is present in intubated patients with COVID-19, at least at some point during the evolution of the disease. Second, low Crs values averaging 35.7 ± 5.8 ml/cm H_2O (in eight consecutive patients with COVID-19 studied at Day 1 after intubation) and 19.58 ± 7.96 ml/cm H_2O (worst respiratory mechanics in 12 patients with COVID-19) were reported by Liu and colleagues (2) and by Pan and colleagues (3), respectively. Despite the claim of preserved elastic properties in COVID-19 pneumonia, these values of Crs are not very different from those reported in patients with ARDS (4, 5), as illustrated in Figure 1. To try to understand the discrepancy in Crs values between these studies and their variability, we have recomputed the individual data reported by Pan and colleagues (3) and found a significant correlation between the level of PEEP used in their patients and Crs (Figure 1A); PEEP levels were determined as the difference between the plateau pressure and the driving pressure. This surprising relationship implies that the lowest PEEP levels were used in patients with the lowest Crs and vice versa. For instance, a PEEP of 4 cm H_2O was used in a patient with a Crs of 12 ml/cm H_2O, whereas another patient with a Crs of 30 ml/cm H_2O was exposed to a PEEP of 15 cm H_2O. In addition, because a significant increase in alveolar P_{CO_2} ($P_{A_{CO_2}}$) was always present as low V_T was used (3), we recomputed alveolar P_{O_2} ($P_{A_{O_2}}$) based on the data available (3). $P_{A_{O_2}}$ was calculated according to the alveolar gas equation using Pa_{CO_2} and $F_{I_{O_2}}$ provided (3), and the gradient Pa_{O_2}–$P_{A_{O_2}}$ was determined. These gradients were greatly deteriorated (Figure 1), as previously reported (1); yet, patients with the lowest compliance were also those with the highest Pa_{O_2}–$P_{A_{O_2}}$ gradient (Figure 1). This indicates that despite an unusual severity of hypoxemia in this population, a coupling between low compliance and high arterial–alveolar O_2 gradient is present in COVID-19–associated respiratory failure. This implies that "sufficient" levels of PEEP should be used in patients with COVID-19–associated respiratory failure and low Crs, as suggested by Figure 1. The optimal level of PEEP should be determined in any given patient by measuring Crs while increasing the PEEP level. Being able to shift the volume–pressure curve of the respiratory system to the right by using the appropriate PEEP may prove to be crucial in these patients. In any case, the levels of optimal PEEP should be determined in every individual patient with COVID-19–associated respiratory failure by considering the minimal level of end-expiratory pressure needed to decrease the driving pressure/volume ratio as shown in Figure 1.

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