# Lung Mechanics in COVID-19 Resemble RDS not ARDS: Could Surfactant be a Treatment?

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To the Editor:

In a recent article to this *Journal*, Gattinoni et al.(1) reported that patients with COVID-19 fulfilling the Berlin criteria of 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 Children's Hospital of Pittsburgh in neonates during the first week of life as part of an IRB approved study of the natural course of respiratory failure in the neonatal period.(2) Twelve prematurely born neonates who were mechanically ventilated due to respiratory distress syndrome (RDS group) were compared to 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 (DFVC) technique that has been described in detail elsewhere.(3) In brief, volume history was established by inflating the lungs to total lung capacity (TLC) with an anesthesia bag system, using a standard inflating pressure of +40 $cmH_2O$. The lungs were then rapidly deflated by opening the endotracheal tube to

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negative pressure reservoir via a 3-way slide valve generating a standard pressure of -40 $cmH_2O$ for up to 3 sec. Pressures of +30 $cmH_2O$ and -30 $cmH_2O$ were used for all neonates weighing <1000gr. The lungs were immediately re-inflated to TLC after the deflation. The produced airflow and integrated volume signals were plotted as a Flow-Volume curve. (Fig. 1) The procedure was repeated until three superimposed curves were obtained. The following indices were calculated: forced vital capacity (FVC), maximum expiratory flow rate at 25% of the FVC (measured from the residual volume) ($MEF_{25}$), and the ratio $MEF_{25}$/FVC. The respiratory system compliance (Crs) was calculated from partial flow-volume curves produced by a modification of the technique described by LeSouef et al.(4) Specifically, the lungs were inflated to TLC and then they were passively deflated from a standard pressure of 10 $cmH_2O$. 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 respiratory system compliance were near normal in RDS. The ratio MEF25/FVC was significantly elevated both in 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 DFVC technique.

Our findings suggest that despite similarities in clinical and often radiographic

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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 non-invasive continuous positive airway pressure (CPAP) even without exogenous surfactant.(6) In contrast, in MAS the surfactant is present but inactivated due to meconium induced inflammation, and its production is impaired due 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 due to extensive alveolar collapse. In that stage adult patients respond to oxygen and non-invasive positive airway pressure in a similar way with 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.

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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.

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LEGENDS

Figure 1. Deflation Flow-Volume Curves in intubated infants. **(A): Term newborn without lung disease**. The outer curves are superimposed DFVCs obtained with inflating pressure of +40 $cmH_2O$ & deflating pressure of -40 cmH2O ; the middle curve is a passive flow-volume curves after the lungs were inflated with a pressure of +40 $cmH_2O$ ; the small inner curve is a passive flow-volume curve from a standard pressure of +10 $cmH_2O$ and it is used to calculate respiratory system compliance and resistance. **(B) & (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.

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| **Table 1. Demographic data & indices of lung mechanics and function** | | | |
|---|---|---|---|
| | **MAS** | **RDS** | **Control** |
| | **n=13** | **n=12** | **n=10** |
| **Postconceptional Age (weeks)** | 39.5 ± 1.9 | 29.0 ± 2.7** | 39.9 ± 0.8 |
| **Postnatal Age (days)** | 3.9 ± 2.0 | 4.0 ± 1.7** | 2.7 ± 2.0 |
| **Weight (grams)** | 3280 ± 397 | 1256 ± 511** | 3174 ± 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 |

*p < 0.001 compared to RDS and to control

**p<0.05 compared to MAS and to control

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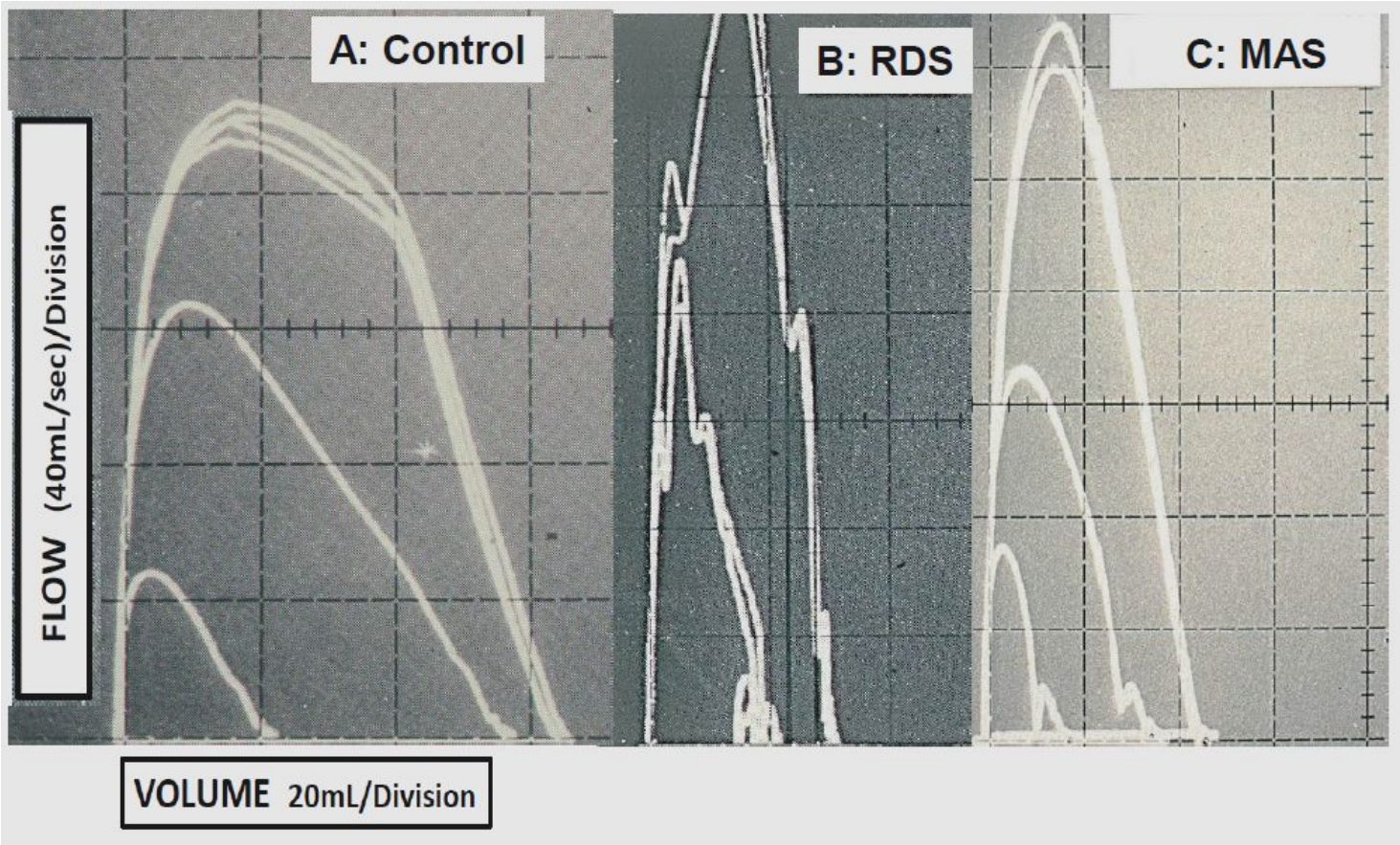
**Figure 1.**

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