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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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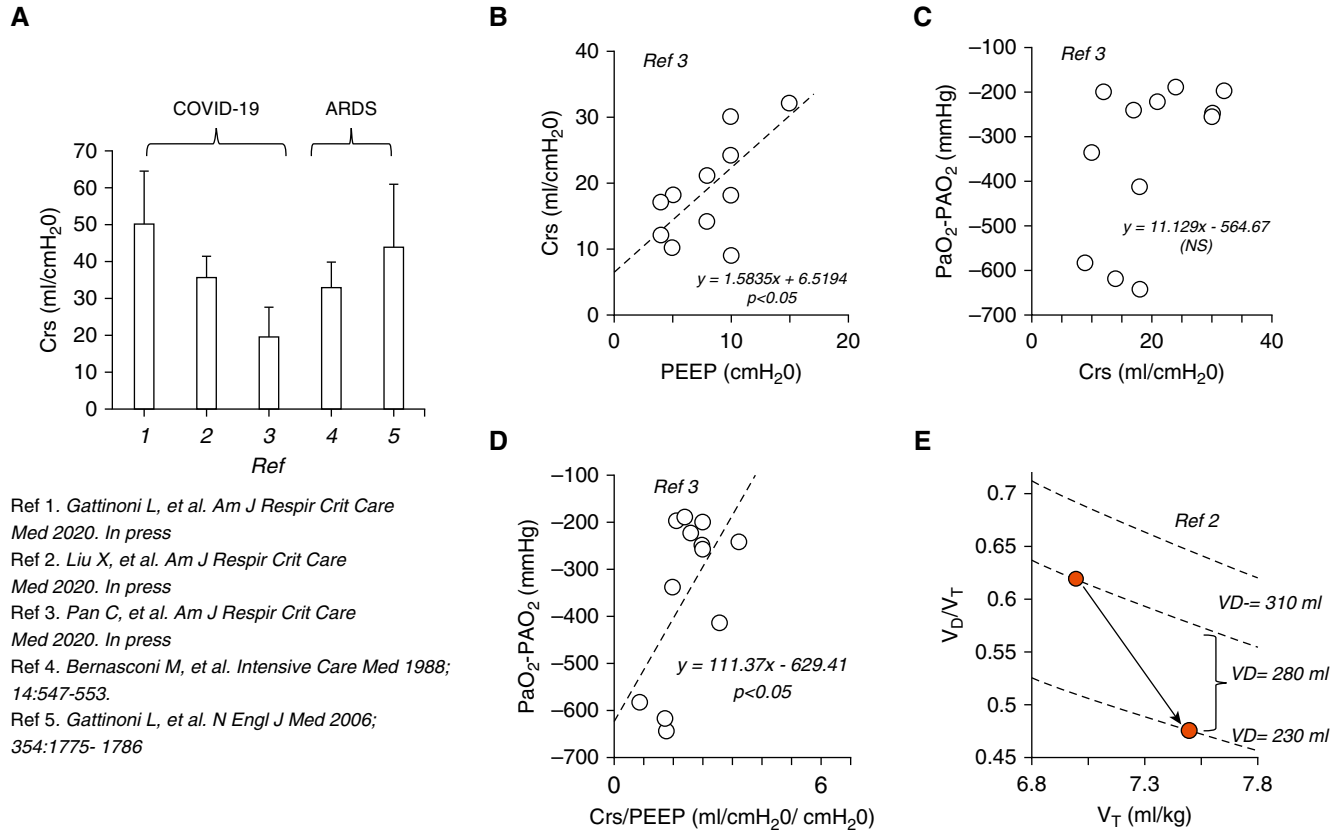

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Figure 1. (*A*) Values of compliance (Crs) collected in mechanically ventilated patients with coronavirus disease (COVID-19) compared with data reported in acute respiratory distress syndrome (the references of the selected studies are given in the figure). Although data were not obtained at the same time of the disease, alterations of the elastic properties of the respiratory system can be significant in all these patients and are not dramatically different between patients with COVID-19 and acute respiratory distress syndrome. (*B*) Relationship between positive end-expiratory pressure (PEEP) and Crs, showing that when low levels of PEEP were used, low Crs was always present (*see* text for comments and discussion). (*C*) Crs versus Pa_{O_2}–alveolar P_{O_2} (PA_{O_2}) gradient. Extreme deterioration of the Pa_{O_2}–PA_{O_2} gradient was observed in many patients; however, although the patients with the lowest Crs have the greatest gradient, the correlation remains weak in this limited population. (*D*) Relationship between the Crs/PEEP ratio and the Pa_{O_2}–PA_{O_2} gradient; the ratio was used as an indicator of the effects of PEEP applied at any given Crs. The patients with the lowest ratio had the highest gradient, with a significant correlation between the two variables. (*E*) Iso–dead space (iso-V_D) curves showing the relationship between V_T and V_D/V_T ratio. By minimally increasing V_T, the change in V_D/V_T ratio and thus in alveolar gas composition improves out of proportion of the changes in serial V_D (*see* text for further comments). ARDS = acute respiratory distress syndrome.

2. Does minimally increasing V_T improve pulmonary gas exchange, or are the COVID-19 lungs nonrecruitable?

Lui and colleagues have shown that increasing V_T from 7 to 7.5 ml/kg produced a significant decrease in Pa_{CO_2} (2). We have reevaluated this question by determining the averaged dead space ventilation ($\dot{V}_D$) in patients receiving a V_T of 7 ml/kg (2). To do so, average alveolar ventilation ($\dot{V}_A$) was calculated from Pa_{CO_2} ($\dot{V}_A = k \times \dot{V}_{CO_2}/Pa_{CO_2}$), and then $\dot{V}_D$ was determined as $\dot{V}_E$ (given in the text) minus $\dot{V}_A$. Based on the average body weight, V_T was computed and then f was determined from the $\dot{V}_E$ values, given in the text. The corresponding dead space (V_D) was computed as $\dot{V}_D$/f. The same computation was performed for a V_T of 7.5 ml/kg. The expected changes in V_D/V_T ratio were then calculated as a function of V_T (Figure 1) at the given V_Ds, creating iso-V_D curves. As shown in Figure 1, when V_T was increased from 7 to 7.5 ml/kg, the decrease in the V_D/V_T ratio was much higher than expected from a monoalveolar model (same iso-V_D curve), reflecting the recruitment of lung regions with high $\dot{V}_A$:$\dot{Q}$ ratio (lowering V_D). These data therefore suggest that at a low "cost" in terms of barotrauma, it is possible via a modest increase in V_T to reduce serial dead space ventilation (as expected) together with a decrease in parallel dead space ventilation.

The phenotype of patients in acute respiratory failure with "COVID lungs" is certainly quite heterogenous; the individual determination of Crs, Pa–PA_{O_2} gradient, and Pa_{CO_2} as a function of the level of PEEP and V_T should be performed in every patient to tailor the optimal modality of ventilation at the different stages of the disease. The short- and long-term impacts of using "larger" V_T together with relatively high PEEP in patients with COVID-19–associated respiratory failure who display a low compliance at low PEEP is fundamental to evaluate. Only such an approach could allow operation with the highest possible compliance and lowest Pa–PA_{O_2} gradient in these patients. ■

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

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Reply by Gattinoni *et al.* to Hedenstierna *et al.*, to Maley *et al.*, to Fowler *et al.*, to Bhatia and Mohammed, to Bos, to Koumbourlis and Motoyama, and to Haouzi *et al.*

From the Authors:

The strong controversies raised by our 400-word letter (1) reflect the underlying conflict through which medical knowledge and science proceed: on one side, the need for evidence regarding a treatment, for which the apex is randomized trials, and on the other side, the need for evidence to elucidate the mechanisms of disease, for which the apex is the reproducible observation of phenomena and their interactions (2). As suggested by Fowler and colleagues, in a pandemic the real problem is to "balance the tradeoff between learning (evidence of mechanism) and doing (evidence of response to treatment)." In any case, the process of acquiring knowledge about a novel disease or treatment ideally begins with observations (generating the hypothesis) and ends with the experiments (to prove or disprove the hypothesis).

However, as evidenced by this correspondence, our scientific community seems divided into two broad categories: On one side are the believers that coronavirus disease (COVID-19) pneumonia must be defined as acute respiratory distress syndrome (ARDS)—and that is it. If so, we have *nothing* to learn about its respiratory treatment, just to do (lung-protective strategy, positive end-expiratory pressure [PEEP]–$F_{I_{O2}}$ table, etc.) (3). On the other side are the believers that COVID-19 is a specific disease that is somehow different from ARDS, with manifestations that may change over time. As such, we have *much* to learn regarding mechanisms and what a "lung-protective" approach should mean in this setting (4).

It is from collecting hundreds of consistent observations (the so-despised anecdotes) from Milan, Parma, Turin, and London that we proposed two phenotypes, which represent the extremes of a broad spectrum of the respiratory manifestations in COVID-19 pneumonia: an early phenotype, L (i.e., the "atypical" ARDS of our letter, characterized by lower elastance, lower $\dot{V}_A/\dot{Q}$, lower recruitability, and lower lung weight), and a late phenotype, H (i.e., the typical ARDS, characterized by higher lung elastance, higher right-to-left shunt, higher recruitability, and higher lung weight) (5).

Dr. Bos, Dr. Maley and colleagues, and Dr. Haouzi and colleagues in their letters conclude, as do many others in our scientific community, that COVID-19 pneumonia is not atypical but fits the conventional ARDS definition and that higher respiratory system compliance (Crs) may be a normal finding in the syndrome. Dr. Bos, in particular, reports a "striking similarity" between the common presentation of patients with severe COVID-19 pneumonia and the ARDS originally described by Ashbaugh in 1967, namely, "acute onset of tachypnea, hypoxemia and loss of compliance." Actually, the L patients presenting to the hospital are in 50% of the cases eupneic, with a respiratory rate of approximately 20 breaths/min (approximately 40 breaths/min in the Ashbaugh paper [6]) with near a normal Crs of >50 ml/cm H_2O (<20 ml/cm H_2 in Ashbaugh [6]).

Maley and colleagues suggest that our small cohort (16 patients with a mean Crs of 50.2 ± 14.3 ml/cm H_2O) cannot meaningfully be compared with the series of Seattle (24 patients with a median Crs of 29 ml/cm H_2O [25–36]). Finally, Haouzi and colleagues critique the large range of Crs values we reported (20–90 ml/cm H_2O). Because the disease is the same all around the world, the observations also should be similar. Actually, we believe that the apparent contradictory results stem from the time of observation, with type L being more likely early on and type H being more likely in the late phase. We suspect that many ICUs are treating patients at a more advanced H stage. The pivotal role of time is demonstrated in Figure 1, in which we show, in a series of 28 patients, that Crs, measured at 5 cm H_2O of PEEP is a function of the days elapsed from the initial symptoms (Figure 1A), regardless the venous admixture (Figure 1B).

The striking feature of the COVID-19 pneumonia in the L state is not the Crs *per se* but the remarkable hypoxemia associated with a lung gas volume far greater than what is found in the ARDS "baby lung." Because the gas and ventilation side are relatively

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