Intensive Care Medicine

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COVID-19 pneumonia: different respiratory treatment for different phenotypes?

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The Surviving Sepsis Campaign panel (ahead of print, DOI: 10.1007/s00134-020-06022-5) recently recommended that "*mechanically ventilated patients with COVID-19 should be managed similarly to other patients with acute respiratory failure in the ICU.*"

Yet, COVID-19 pneumonia [1], despite falling in most of the circumstances under the Berlin definition of ARDS [2], is a specific disease, whose distinctive features are severe hypoxemia often associated with near normal respiratory system compliance (more than 50% of the 150 patients measured by the authors and further confirmed by several colleagues in Northern Italy). This remarkable combination is almost never seen in severe ARDS. These severely hypoxemic patients despite sharing a single etiology (SARS-CoV-2) may present quite differently from one another: normally breathing ("silent" hypoxemia) or remarkably dyspneic; quite responsive to nitric oxide or not; deeply hypocapnic or normo/ hypercapnic; and either responsive to prone position or not. Therefore, the same disease actually presents itself with impressive non-uniformity.

Based on detailed observation of several cases and discussions with colleagues treating these patients, we hypothesize that the different COVID-19 patterns found at presentation in the emergency department depend on the interaction between three factors: 1) the severity of the infection, the host response, physiological reserve and comorbidities; 2) the ventilatory responsiveness of the patient to hypoxemia; 3) the time elapsed between the onset of the disease and the observation in the hospital. The interaction between these factors leads to the development of a time-related disease spectrum within two primary "phenotypes": **Type L**, characterized by **L**ow elastance (i.e., high compliance), **L**ow ventilation to perfusion ratio, **L**ow lung weight and **L**ow recruitability and **Type H**, characterized by **H**igh elastance, **H**igh right-to-left shunt, **H**igh lung weight and **H**igh recruitability.

COVID-19 pneumonia, Type L

At the beginning, COVID-19 pneumonia presents with the following characteristics:

- Low elastance: the nearly normal compliance indicates that the amount of gas in the lung is nearly normal [3].
- Low ventilation to perfusion (VA/Q) ratio: since the gas volume is nearly normal, hypoxemia may be best explained by the loss of regulation of perfusion and by loss of hypoxic vasoconstriction. Accordingly, at this stage, the pulmonary artery pressure, should be near normal.
- Low lung weight: Only ground-glass densities are present on CT scan, primarily located subpleurally and along the lung fissures. Consequently, lung weight is only moderately increased.
- Low lung recruitability: the amount of non-aerated tissue is very low, consequently the recruitability is low [4].

To conceptualize these phenomena, we hypothesize the following sequence of events: the viral infection leads to a modest local subpleural interstitial edema (ground-glass lesions) particularly

located at the interfaces between lung structures with different elastic properties, where stress and strain are concentrated [5]. Vasoplegia accounts for severe hypoxemia. The normal response to hypoxemia is to increase minute ventilation, primarily by increasing the tidal volume [6] (up to 15-20 ml/kg), which is associated with a more negative intrathoracic inspiratory pressure. Undetermined factors other than hypoxemia, markedly stimulate, in these patients, the respiratory drive. The near normal compliance, however, explains why some of the patients present without dyspnea as the patient inhales the volume he expects. This increase in minute ventilation leads to a decrease in $PaCO_2$.

The evolution of the disease: transitioning between phenotypes

The Type L patients may remain unchanging for a period and then improve or worsen the possible key feature which determines the evolution of the disease - other than the severity of the disease itself, is the depth of the negative intrathoracic pressure associated with the increased tidal volume in spontaneous breathing. Indeed, the combination of a negative inspiratory intrathoracic pressure and increased lung permeability due to inflammation, results in interstitial lung edema. This phenomenon, initially described by Barach in 1938 [7] and Mascheroni in 1988 [8] both in an experimental setting, has been recently recognized as the leading cause of Patient - Self Inflicted Lung Injury (P-SILI) [9]. Over time, the increased edema increases lung weight, superimposed pressure, and dependent atelectasis. When lung edema reaches a certain magnitude, the gas volume in the lung decreases , and the tidal volumes generated for a given inspiratory pressure decrease [10]. At this stage, dyspnea develops, which in turn leads to worsening P-SILI. The transition from Type L to Type H may be due to the evolution of the COVID-19 pneumonia on one hand and the injury attributable to high-stress ventilation on the other.

COVID-19 pneumonia, Type H

The Type H patient

- High elastance: The decrease of gas volume due to increased edema accounts for the increased lung elastance.
- High right-to-left shunt: This is due to the fraction of cardiac output perfusing the non-aerated tissue which develops in the dependent lung regions due to the increased edema and superimposed pressure.
- High lung weight: Quantitative analysis of the CT scan shows a remarkable increase in lung weight (> 1.5 kg), on the order of magnitude of severe ARDS [11].
- High lung recruitability: The increased amount of non-aerated tissue is associated, as in severe ARDS, with increased recruitability [12].

The Type H pattern, 20 – 30% of patients in our series, fully fits the severe ARDS criteria: hypoxemia, bilateral infiltrates, decreased the respiratory system compliance, increased lung weight and potential for recruitment. Figure 1 summarizes the time course we described. In Panel A, we show the CT in

spontaneous breathing of a Type L patient at admission and, in Panel B, its transition in Type H after 7 days of non invasive support. As shown, a similar degree of hypoxemia was associated to different patterns in lung imaging.

Respiratory treatment

Given this conceptual model, it follows that the respiratory treatment offered to Type L and Type H patients must be different. The proposed treatment is consistent with what observed in COVID-19, even though the overwhelming number of patients seen in this pandemic may limit its wide applicability.

1. The first step to reverse hypoxemia is through an increase in FiO_2 to which the Type L patient respond wells, particularly if not yet breathless.
2. In Type L patients with dyspnea, several non-invasive options are available: High Flow Nasal Cannula (HFNC), Continuous Positive Airway Pressure (CPAP) or Non Invasive Ventilation (NIV). At this stage the measurement (or the estimation) of the inspiratory esophageal pressure swings is crucial [13]. In the absence of the esophageal manometry, surrogate measures of work of breathing, such as the swings of central venous pressure [14], or clinical detection of excessive inspiratory effort should be assessed. In intubated patients the P0.1 and P occlusion should also be determined. High PEEP, in some patients, may decrease the pleural pressure swings and stop the vicious cycle that exacerbates lung injury. However, high PEEP in patients with normal compliance may have detrimental effects on hemodynamics. In any case, non-invasive options are questionable, as they may be associated with high failure rates and delayed intubation, in a disease which typically lasts several weeks.
3. The magnitude of inspiratory pleural pressures swings may determine the transition from the Type L to the Type H phenotype. As esophageal pressure swings increase from 5-10 cmH_2O – which are generally well tolerated – to above 15 cmH_2O, the risk of lung injury increases and therefore intubation should be performed as soon as possible.
4. Once intubated and deeply sedated, the Type L patients, if hypercapnic, can be ventilated with volumes greater than 6 ml/kg (up to 8-9 ml/kg). as the high compliance results in tolerable strain without the risk of VILI. Prone positioning should be used only as a rescue maneuver, as the lung conditions are "too good" for the prone position effectiveness, which is based on improved stress and strain redistribution. The PEEP should be reduced to 8-10 cmH_2O, given that the recruitability is low and the risk of hemodynamic failure increases at higher levels. An early intubation may avert the transition to Type H phenotype.
5. Type H patients, should be treated as severe ARDS, including higher PEEP, if compatible with hemodynamics, prone positioning and extracorporeal support.

In conclusion, Type L and Type H patients are best identified by CT scan and are affected by different pathophysiological mechanisms. If not available, signs which are implicit in Type L and Type H defintinon could be used as surrogates: respiratory system elastance and recruitability. Understanding the correct pathophysiology is crucial to establishing the basis for appropriate treatment.

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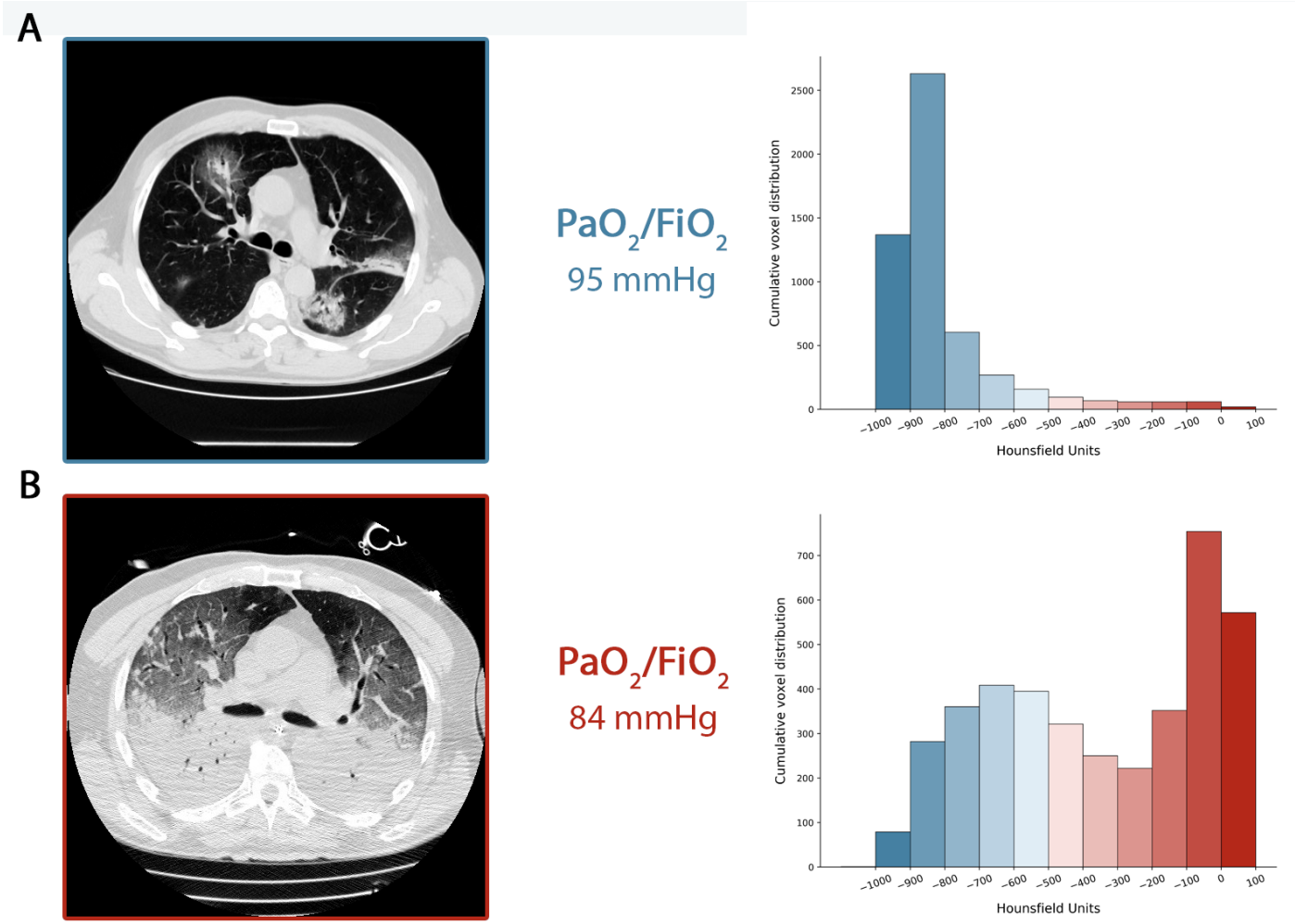
Figure 1



Panel A: CT scan acquired during spontaneous breathing. The cumulative distribution of the CT number is shifted to the left (well aerated compartments), being the 0 to -100 HU compartment, the non-aerated tissue virtually 0. Indeed, the total lung tissue weight was 1108 g, 7.8% of which was not aerated and the gas volume was 4228 ml. Patient receiving oxygen with Venturi mask, inspired oxygen fraction of 0.8.

Panel B: CT acquired during mechanical ventilation at end-expiratory pressure at 5 cmH_2O of PEEP. The cumulative distribution of the CT scan is shifted to the right (non-aerated compartments) while the left compartments are greatly reduced. Indeed, the total lung tissue weight was 2744 g, 54% of which was not aerated and the gas volume was 1360 ml. The patient was ventilated in Volume Controlled mode, 7.8 ml/kg of tidal volume, respiratory rate of 20 breaths per minute, inspired oxygen fraction of 0.7

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COVID-19 pneumonia: ARDS or not?

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Even though it can meet the ARDS Berlin definition [1, 2], the COVID-19 pneumonia is a specific disease with peculiar phenotypes. Its main characteristic is the dissociation between the severity of the hypoxemia and the maintenance of relatively good respiratory mechanics. Indeed, the median respiratory system compliance is usually around 50 ml/cmH_2O. Of note, the patients with respiratory compliance lower or higher than the median value experience hypoxemia of similar severity. We propose the presence of two types of patients ("non-ARDS," type 1, and ARDS, type 2) with different pathophysiology. When presenting at the hospital, type 1 and type 2 patients are clearly distinguishable by CT scan (Fig. 1). If the CT scan is not available, the respiratory system compliance and possibly the response to PEEP are the only imperfect surrogates we may suggest.

Type 1: Near normal pulmonary compliance with isolated viral pneumonia

In these patients, severe hypoxemia is associated with respiratory system compliance > 50 ml/cmH_2O. The lung's gas volume is high, the recruitability is minimal, and the hypoxemia is likely due to the loss of hypoxic pulmonary vasoconstriction and impaired regulation of pulmonary blood flow. Therefore, severe hypoxemia is primarily due to ventilation/perfusion (V_A/Q) mismatch. High PEEP and prone positioning do not improve oxygenation through recruitment of collapsed areas, but redistribute pulmonary perfusion, improving the V_A/Q relationship. Lung CT scans in those patients confirm that there are no significant areas to recruit, but the right-to-left venous admixture is typically around 50%.

Type 2: Decreased pulmonary compliance

In 20–30% of these COVID-19 patients admitted to the intensive care unit (ICU), severe hypoxemia is associated with compliance values < 40 ml/cmH_2O, indicating severe ARDS [3]. It is certainly possible that their lower compliance (i.e., lower gas volume and increased recruitability) is due to the natural evolution of the disease, but we cannot exclude the possibility that this severity of damage (increased edema) results in part from the initial respiratory management. Indeed, some of these hypoxemic patients receive CPAP or non-invasive ventilation before ICU admission and present with very high respiratory drives, vigorous inspiratory efforts, and highly negative intrathoracic pressures. Therefore, in addition to viral pneumonia, those patients likely have self-inflicted ventilator-induced lung injury [4].

Clinical implications

Before ICU, in non-intubated patients

CPAP and NIV are the first-line treatment when an overwhelming number of patients come to a hospital. These interventions, often applied outside the ICU in emergency rooms or in other medicine wards, usually improve blood oxygenation. A key aspect of care, however, should be the assessment of respiratory drive and the inspiratory efforts. The ideal indicator would be the measurement of the esophageal pressure swings. If impossible, the clinical signs of inspiratory efforts should be carefully scrutinized. If respiratory distress is present, endotracheal intubation should be strongly considered to avoid/limit the transition from type 1 to type 2 by self-induced lung injury.

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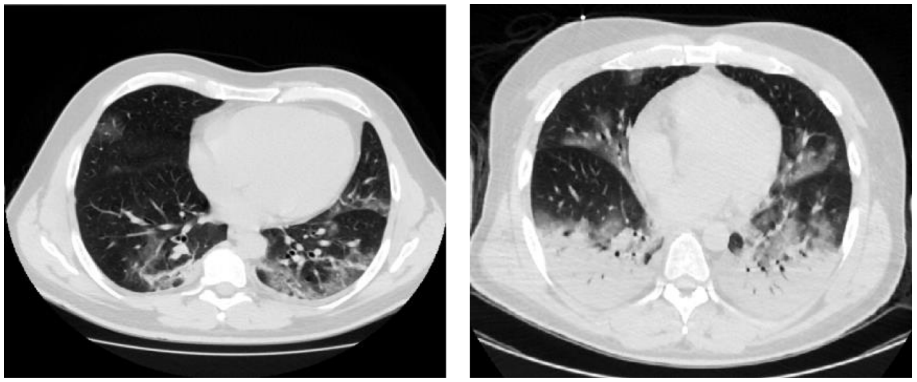

Fig. 1 In these 2 patients were recorded the following variables: type 1 lung weight (1192 g), gas volume (2774 ml), percentage of non-aerated tissue (8.4%), venous admixture (56%), P/F (68), and respiratory system compliance (80 ml/cmH_2O); type 2 lung weight (1441 g), gas volume (1640 ml), percentage of non-aerated tissue (39%), venous admixture (49%), P/F (61), and respiratory system compliance (43 ml/cmH_2O)

In ICU, intubated patients

Tidal volume

In type 2 patients, a lower tidal volume should be applied. However, type 1 patients lack the low compliance/high driving pressure prerequisites of ventilator-induced lung injury, even if treated with volumes higher than 6 ml/kg delivered at respiratory rates of 15–20 breaths/min [5]. More liberal tidal volume (7–8 ml/kg) often attenuates dyspnea and may avoid hypoventilation with possible reabsorption atelectasis and hypercapnia.

PEEP

The type 1 patients lack the prerequisite for higher PEEP to work (recruitability). PEEP levels should be limited at 8–10 cmH_2O, since higher levels will decrease pulmonary compliance and can impact right heart function. The type 2 patients are characterized by a reduction of total gas volume and an increase in lung weight and edema. These features may be due to the natural progression of the disease, to bacterial superinfection and/or to self-induced lung injury during the period preceding the intubation. In these patients, a cautious gradual increase of PEEP up to 14–15 cmH_2O may be beneficial. A decrease in SvO2 during this phase suggests an inadequate cardiac output so that higher PEEP levels for lung recruitment may no longer be useful. Cardiac ultrasound may also be useful for assessing right heart function when increasing PEEP levels.

Shunt determination

Calculating the shunt fraction is the best tool to assess oxygenation.

The $etCO_2/PaCO_2$ relationship is a useful tool to quantify efficiency of pulmonary exchange. A ratio < 1 suggests elevated shunt and dead space (areas of lung ventilated and not perfused).

Prone positioning For type 2 patients, prone position could be used as a long-term treatment—as in any form of severe ARDS [6, 7]. However, in type 1 patients, prone positioning should be considered more as a *rescue* maneuver to facilitate the redistribution of pulmonary blood flow, rather than for opening collapsed areas. Long-term prone positioning/supine cycles is of very little benefit in patients with high lung compliance, and it leads to high levels of stress and fatigue in the personnel.

Nitric oxide The oxygenation response to NO is variable. The COVID-19 pneumonia appears to interfere with the vascular regulation up to complete loss of vascular tone to vasoconstricting or vasodilating agents. We still do not have enough evidence to understand when and on which patients it should be applied. Nitric oxide should not work in fully vasoplegic patients (type 1 in our model) but possibly works in patients in which pulmonary hypertension is more likely (type 2 in our model).

(Micro)thrombosis and D-dimer levels In this disease, thrombosis and associated ischemic events are very common. A daily check of coagulation parameters, in particular D-dimer levels, should be performed in both the type 1 and the type 2 patients, judiciously anticoagulated when indicated.

Type 1 patients:

- PEEP levels should be kept lower in patients with high pulmonary compliance
- Tidal volume thresholds should not be limited at 6 ml/kg
- Respiratory rate should not exceed 20 breaths/min
- Patients should be left “quiet”; avoiding doing too much is of higher benefit than intervening at any cost.

Type 2 patients:

- Standard treatment for severe ARDS should be applied (lower tidal volume, prone positioning, and relatively high PEEP).

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Publisher's Note

Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome

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Dear Editor,

In northern Italy an overwhelming number of patients with Covid-19 pneumonia and acute respiratory failure have been admitted to our Intensive Care Units. Attention is primarily focused on increasing the number of beds, ventilators and intensivists brought to bear on the problem, while the clinical approach to these patients is the one typically applied to severe ARDS, namely high Positive End Expiratory Pressure (PEEP) and prone positioning. However, the patients with Covid-19 pneumonia, fulfilling the Berlin criteria of ARDS, present an atypical form of the syndrome. Indeed, the primary characteristics we are observing (confirmed by colleagues in other hospitals), is the dissociation between their relatively well preserved lung mechanics and the severity of hypoxemia. As shown in our first 16 patients (Figure 1), the respiratory system compliance of 50.2 ± 14.3 ml/cmH_2O is associated with shunt fraction of 0.50 ± 0.11. Such a wide discrepancy is virtually never seen in most forms of ARDS. Relatively high compliance indicates well preserved lung gas volume in this patient cohort, in sharp contrast to expectations for severe ARDS.

A possible explanation for such severe hypoxemia occurring in compliant lungs is the loss of lung perfusion regulation and hypoxic vasoconstriction. Actually, in ARDS, the ratio between the shunt fraction to the fraction of gasless tissue is highly variable, with mean 1.25 ± 0.80(1). In eight of our patients with CT scan, however, we measured a ratio of 3.0 ± 2.1, suggesting remarkable *hyper*perfusion of gasless tissue. If so, the oxygenation increases with high PEEP and/or prone position are not primarily due to recruitment, the usual mechanism in ARDS(2), but instead, in these patients with a poorly recruitable pneumonia(3), to the redistribution of perfusion in response to pressure and/or gravitational forces. We should consider that:

1. Patients treated with Continuous Positive Airway Pressure or Non Invasive Ventilation, presenting with clinical signs of excessive inspiratory efforts, intubation should be prioritized to avoid excessive intrathoracic negative pressures and self-inflicted lung injury(4).

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2. High PEEP in a poorly recruitable lung tends to result in severe hemodynamic impairment and fluid retention;

3. Prone positioning of patients with relatively high compliance results in a modest benefit at the price of a high demand for stressed human resources.

After considering that, all we can do ventilating these patients is "buying time" with minimum additional damage: the lowest possible PEEP and gentle ventilation. We need to be patient.

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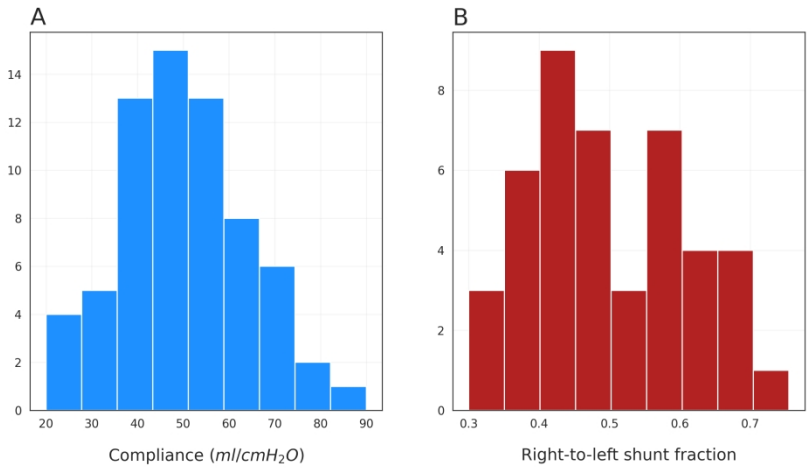

Figure 1

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ARDS with COVID-19. An intermediate V_T (7–8 ml/kg PBW) ventilation strategy was applied to the first four patients to increase pulmonary efficiency to eliminate CO_2, and this was used in the next four patients.

Gas exchange consists of oxygenation and ventilation. Oxygenation is quantified by the Pa_{O_2}/FI_{O_2} ratio, and this method has gained wide acceptance, particularly since publication of the Berlin definition of ARDS (7). However, the Berlin definition does not include additional pathophysiological information about ARDS, such as alveolar ventilation, as measured by pulmonary dead space, which is an important predictor of outcome (8). Increased pulmonary dead space reflects the inefficiency of the lungs to eliminate CO_2, which may lead to hypercapnia.

In our patients with ARDS with COVID-19, hypercapnia was common at ICU admission with low V_T ventilation. Assuming the anatomic portion of dead space is constant, increasing V_T with constant respiratory rate would effectively increase alveolar ventilation. Any such increase in V_T would decrease Pa_{CO_2}, which would be captured by VR (6). VR, a novel method to monitor ventilatory adequacy at the bedside (4–6), was very high in our patients, reflecting increased pulmonary dead space and inadequacy of ventilation.

With an acceptable plateau pressure and driving pressure, titration of V_T was performed. Pa_{CO_2} and VR were significantly decreased when an intermediate V_T (7–8 ml/kg PBW) was applied. We suggest that intermediate V_T (7–8 ml/kg PBW) is recommended for such patients. Therefore, low V_T may not be the best approach for all patients with ARDS, particularly those with a less severe decrease in respiratory system compliance and inadequacy of ventilation.

In summary, we found that hypercapnia was common in patients with COVID-19–associated ARDS while using low V_T ventilation. VR was increased in these patients, which reflected increased pulmonary dead space and inadequacy of ventilation. An intermediate V_T was used to correct hypercapnia efficiently, while not excessively increasing driving pressure. Clinicians must have a high index of suspicion for increased pulmonary dead space when patients with COVID-19–related ARDS present with hypercapnia. ■

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COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome

To the Editor:

In northern Italy, an overwhelming number of patients with coronavirus disease (COVID-19) pneumonia and acute respiratory failure have been admitted to our ICUs. Attention is primarily focused on increasing the number of beds, ventilators, and intensivists brought to bear on the problem, while the clinical approach to these patients is the one typically applied to severe acute respiratory distress syndrome (ARDS), namely, high positive end-expiratory pressure (PEEP) and prone positioning. However, the patients with COVID-19 pneumonia, despite meeting the Berlin definition of ARDS, present an atypical form of the syndrome. Indeed, the primary characteristic we are observing (and has been confirmed by colleagues in other hospitals) is a dissociation between their relatively well-preserved lung mechanics and the severity of hypoxemia. As shown in our first 16 patients (Figure 1), a respiratory system compliance of 50.2 ± 14.3 ml/cm H_2O is associated with a shunt fraction of 0.50 ± 0.11. Such a wide discrepancy is virtually never seen in most forms of ARDS. Relatively high compliance indicates a

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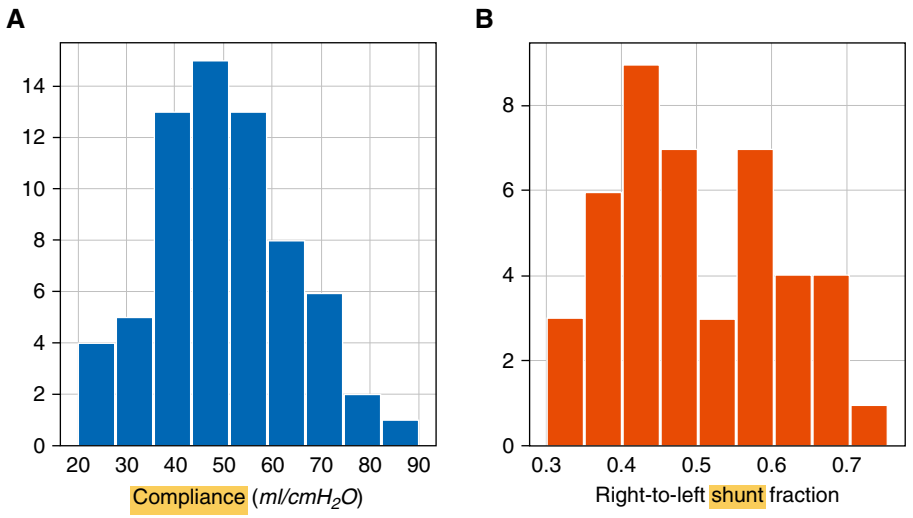

Figure 1. (*A*) Distributions of the observations of the compliance values observed in our cohort of patients. (*B*) Distributions of the observations of the right-to-left shunt values observed in our cohort of patients.

well-preserved lung gas volume in this patient cohort, in sharp contrast to expectations for severe ARDS.

A possible explanation for such severe hypoxemia occurring in compliant lungs is a loss of lung perfusion regulation and hypoxic vasoconstriction. Actually, in ARDS, the ratio of the shunt fraction to the fraction of gasless tissue is highly variable, with a mean of 1.25 ± 0.80 (1). In eight of our patients with a computed tomography scan, however, we measured a ratio of 3.0 ± 2.1, suggesting a remarkable *hyper*perfusion of gasless tissue. If this is the case, the increases in oxygenation with high PEEP and/or prone positioning are not primarily due to recruitment, the usual mechanism in ARDS (2), but instead, in these patients with poorly recruitable lungs (3), result from the redistribution of perfusion in response to pressure and/or gravitational forces. We should consider that *1*) in patients who are treated with continuous positive airway pressure or noninvasive ventilation and who present with clinical signs of excessive inspiratory efforts, intubation should be prioritized to avoid excessive intrathoracic negative pressures and self-inflicted lung injury (4); *2*) high PEEP in a poorly recruitable lung tends to result in severe hemodynamic impairment and fluid retention; and *3*) prone positioning of patients with relatively high compliance provides a modest benefit at the cost of a high demand for stressed human resources.

Given the above considerations, the best we can do while ventilating these patients is to "buy time" while causing minimal additional damage, by maintaining the lowest possible PEEP and gentle ventilation. We need to be patient. ■

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

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Reply to: Hedenstierna et al, Haouzi et al, Maley et al, Fowler et al, Bhatia and Mohammed, Bos, & Koumbourlis and Motoyama

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To the Editor:

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, whose apex are the randomized trials; on the other side, the need for evidence to elucidate the mechanisms of disease, whose apex is the reproducible observation of phenomena and their interactions (2). As suggested by Fowler et al, 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 the believers that COVID-19 pneumonia must be defined as ARDS - and that is it. If so, we have *nothing* to learn about its respiratory treatment, just to do (lung protective strategy, PEEP-FiO_2 table etc.) (3). On the other side, the believers that COVID-19 is a specific disease, somehow different from ARDS, whose manifestations 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).

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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 V_A/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, Maley and Haouzi 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 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 around 20 bpm (around 40 bpm in Ashbaugh paper), with near a normal Crs > 50 ml/cmH_2O (< 20 ml/cmH_2O in Ashbaugh).

Maley et al suggest that our small cohort (16 patients, mean Crs of 50.2 ± 14.3 ml/cmH_2O) cannot meaningfully be compared with the series of Seattle (24 patients, median Crs of 29

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ml/cmH_2O [25 -36] ml/cmH_2O). Finally, Haouzi et al critique the large range of the Crs values we reported (20-90 ml/cmH_2O). As 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, Type **L** being more likely early on and Type **H** 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 cmH_2O of PEEP, is a function of the days elapsed from the initial symptoms (Panel A), regardless the venous admixture (Panel B).

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". As the gas and ventilation side are relatively preserved, the hypoxemia must primarily derive from the perfusion side (6). Indeed, a growing number of observations show endothelial involvement (7), that initiates hypercoagulability (8) and the lung perfusion dysregulation that causes severe hypoxemia due to V_A/Q mismatch. However, as pointed out by Bhatia, microthrombosis are likely part of this phenomenon. In this context Hedenstierna et al. suggested that inhaled nitric oxide (iNO) could be of interest to correct hypoxemia. This is rational and certainly possible, but only further observations may tell us the value of iNO in the different stages of the disease. Given that the hypoxemia is mainly determined by a pathology

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on the endothelial side of the alveolar membrane, the use of exogenous surfactant suggested by Koumbourlis lacks physiological rationale.

Thus, so far, we have learned that COVID-19 is a systemic disease in which the viral assault is primarily focused on the endothelium, which accounts both for the pulmonary vascular dysregulation and the hypercoagulable state. Are these insights sufficient to rethink and change our practice, and if so, at which stage? Fowler et al, recognizing the difficulties to promptly organize RCTs, propose direct acyclic graph to evaluate the hypothetical risks and benefits of conventional therapies for the two extreme phenotypes. In the meantime, how should we manage type **L** patient? The transition from **L** to **H** status -*where the ARDS criteria and therapies fully apply*, may be due both to the natural course of the disease and to the patient's Patient – Self Induced Lung Injury (P-SILI) (9). There is little that can be done to alleviate the first factor, but we can certainly intervene to prevent P-SILI. If, despite non-invasive support, the patient continues to make vigorous inspiratory efforts, we believe that mechanical ventilation should be applied without delay. During mechanical ventilation of these early phase **L** patients, higher PEEP is not advisable despite the severe hypoxemia, as recruitability is relatively low, the lung is already full of gas, and the consequences on hemodynamics may be remarkable. We also proposed, in these **L** patients, a tidal volume higher than 6 ml/kg, provoking a strong disagreement by Maley et.al, for whom the

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conventionally low tidal volume ventilation is the precise strategy for gentle lung ventilation. However, in those patients with higher Crs, the tradeoff is between possible Ventilator-Induced Lung Injury (VILI) and possible hypoventilation, with increased need for sedation and risk of atelectasis. We believe that in the **L** patients the risk of VILI is minimized, as plateau, driving pressure and mechanical power are far from their conventionally accepted thresholds. In addition, we would like to respectfully remind our correspondents that in three large RCTs, no differences were found between patients treated with 7.1 vs 10.3 ml/kg IBW (10), 7.2 vs 10.8 ml/kg IBW (11), 7.3 vs 10.2 ml/kg IBW (12).

ARDS is of fundamental importance in ICU community, which developed in parallel to the understanding of the syndrome (13). Many people have argued that the term 'ARDS' is too generic as it encompasses too many conditions and etiologies to have any credible diagnostic and prognostic validity. It is therefore ironic to see how many try to turn strongly in favor of preserving the diagnosis of ARDS in the COVID-19 disease. Particularly as COVID-19 is a single-etiology disease (unlike ARDS) and the ventilatory management is independent from the degree of hypoxemia (unlike ARDS). Standard ARDS treatment, in such cases should be deeply reconsidered, taking also in account that the mortality rate in different ICU around the world ranges from 10 to 90% (personal communications). Because the disease is the same, this disparity underlines the impact of treatment.

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Figure Legend

Figure 1

Panel A: Respiratory system compliance, measured at 5 cmH2O of PEEP, within 48 hours after admission in Intensive Care Unit, as a function of the days elapsed since symptoms onset ($p < 0.001$).

Panel B: Venous admixture fraction, measured in the same conditions, as a function of the days elapsed since symptoms onset ($p = 0.964$).

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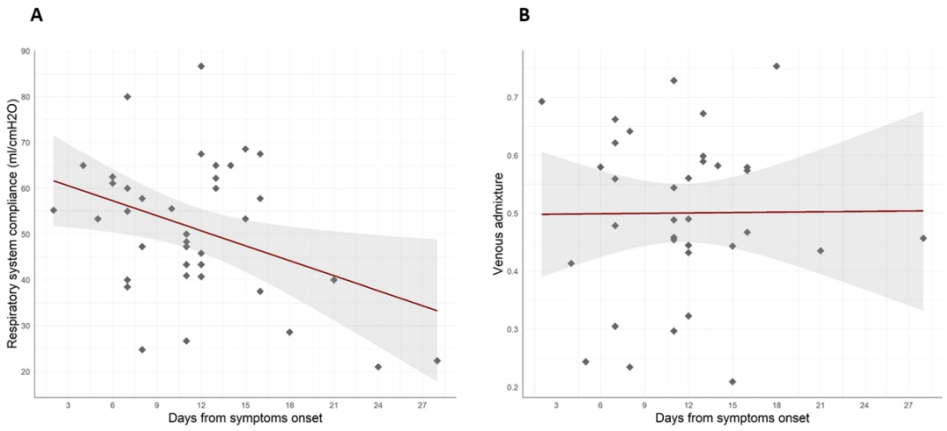

Panel A: Respiratory system compliance, measured at 5 cmH2O of PEEP, within 48 hours after admission in Intensive Care Unit, as a function of the days elapsed since symptoms onset ($p < 0.001$).
Panel B: Venous admixture fraction, measured in the same conditions, as a function of the days elapsed since symptoms onset ($p = 0.964$).

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Treatment of COVID-19 by Inhaled NO to Reduce Shunt?

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Dear Editor,

We read with interest the letter by Gattinoni and co-authors on their CT findings in COVID-19 patients. They found a dramatic increase in the ratio between the shunt fraction to the fraction of gasless tissue, the ratio being almost three times higher than what they have seen in "typical" ARDS (1). They suggested this to be a "remarkable hyperperfusion of gasless tissue". COVID-19 patients do present with very low oxygenation ratio (PaO_2/F_IO_2), as for example in a study from Wuhan, China, with a median of 77 mmHg and a mortality rate of more than 60% (2). Interestingly, the PaO_2/F_IO_2 ratio was also very low in a previous coronavirus infection, the SARS 2002-2003 with a PaO_2/F_IO_2 of 110 mmHg in one study (3). This may possibly be related to the binding of SARS Coronavirus to the ACE-2 protein that is present in endothelial cells (4), impeding hypoxic pulmonary vasoconstriction. This should increase perfusion of gasless tissue, even to the extent of calling it "hyperperfusion". It may be speculated that a similar mechanism exists also in COVID-19.

Gattinoni and co-authors concluded that continuous positive airway pressure, or high positive end-expiratory pressure may worsen the condition, and that prone position may be less successful in these patients (1). What, however, was not discussed is whether blood flow can be reduced in the gasless (atelectatic, fluid-filled, consolidated) tissue, thereby reducing shunt. One of the authors of this letter treated SARS patients in Beijing 2003 with inhaled nitric oxide (5). The inhaled nitric oxide is distributed to ventilated lung regions, dilating vessels and redistributing perfusion to these regions away from gasless, non-ventilated lung regions. The Beijing results were rather dramatic with a PaO_2/F_IO_2 ratio increasing from 97 to 260 mmHg, much more than seen when inhaled nitric oxide has been provided in "typical" ARDS. This suggests marked decrease of perfusion in gasless lung regions (5). In addition, large lung infiltrates seen on chest x-ray decreased within a few days. Neither the PaO_2/F_IO_2 ratio, nor chest x-ray findings improved in a control group without inhaled nitric oxide.

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Moreover, an antiviral effect was seen in cell culture tests when a nitric oxide donor, S-nitroso-N-acetylpenicillamine, SNAP, was added to the cell culture (6).

These findings may make inhaled nitric oxide of interest also in the treatment of COVID-19. It may be that treatment should start as early as possible after the patient has been connected to a ventilator, realizing that when a "septic storm" has begun and multiorgan failure is developing, any treatment is likely to falter.

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Reply by Xu et al: Haouzi et al.

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To the Editor

Globally, numerous patients with COVID-19 develop ARDS and require mechanical ventilation (1-3). Great attention is paid to the respiratory pathophysiology of COVID-19, which potentially leads to “atypical” ARDS (4). A recent study by HAOUZI et al. re-analyzed the data from newly published case series reporting the lung mechanics of COVID-19 (4-6) and found enormous heterogeneity of COVID-19 related ARDS (ref). In our previous study, hypercapnia was common when using low tidal volume ventilation in such ARDS patients (5). Elevated pulmonary dead space in these patients was captured by ventilatory ratio (VR) and reinforced by HAOUZI et al (ref). Reports have indicated that increased dead space is independently associated with an increased risk of death in ARDS patients (7). In addition, optimal positive end-expiratory pressure (PEEP) should be achieved at the highest compliance with the lowest dead space fraction individually, thus PEEP titration and lung recruitment can be guided through measuring dead space (8). Moreover, prone positioning was proven to improve oxygenation and CO_2 clearance by recruitment of dorsal lung units and redistribution of ventilation and perfusion (9, 10), suggesting dead space may be useful for assessing the benefits of prone positioning. Ziehr et al. have reported an improvement in terms of oxygenation and compliance with prone positioning in COVID-19 related ARDS patients with an estimated physiologic dead space ratio of 0.45 (11).

Therefore, calculating a simple bedside index of VR to guide the personalized

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ventilation is highly recommended given the importance of pulmonary dead space in the management of COVID-19 related ARDS.

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COVID-19 Related Acute Respiratory Distress Syndrome: Not so Atypical

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Words: 607/600

A short running head: Severe COVID19: not atypical.

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To the editor,

Patients infected with the SARS-CoV2 virus frequently develop 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 V/Q [2]. Treatment recommendations that have been based on conceptional physiological models resulting from these observations go against long standing evidence based interventions such as low tidal volume 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 compliance of the respiratory system (Crs) of intubated COVID19 patients ranged between 30-50 mL/cmH2O in two recent series [1, 3]. These values are actually comparable to those reported in LUNG-SAFE, the largest observational cohort study to date [4]. While patients with non-COVID-19 related ARDS do frequently not show signs of DAD on autopsy [5], the available autopsy reports of patients who died from COVID19 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 realise that

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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 hyper-inflammation might respond different to higher end-expiratory pressure, restrictive fluid management or immunomodulation with simvastatin treatment while patients with a non-focal lung morphology benefit more from recruitment than prone positioning [8, 9]. However, no one is advocating for implementing these personalised 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. COVID19-related ARDS is an etiological subphenotype of ARDS with a particular set of characteristics: frequent DAD, (possibly) a higher than expected Crs, low PaO2/FiO2 values, frequent non-focal 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 realise that there is no “typical ARDS”.

Despite the described heterogeneity that is inherent to the syndromic definition of ARDS, low tidal volume 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

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

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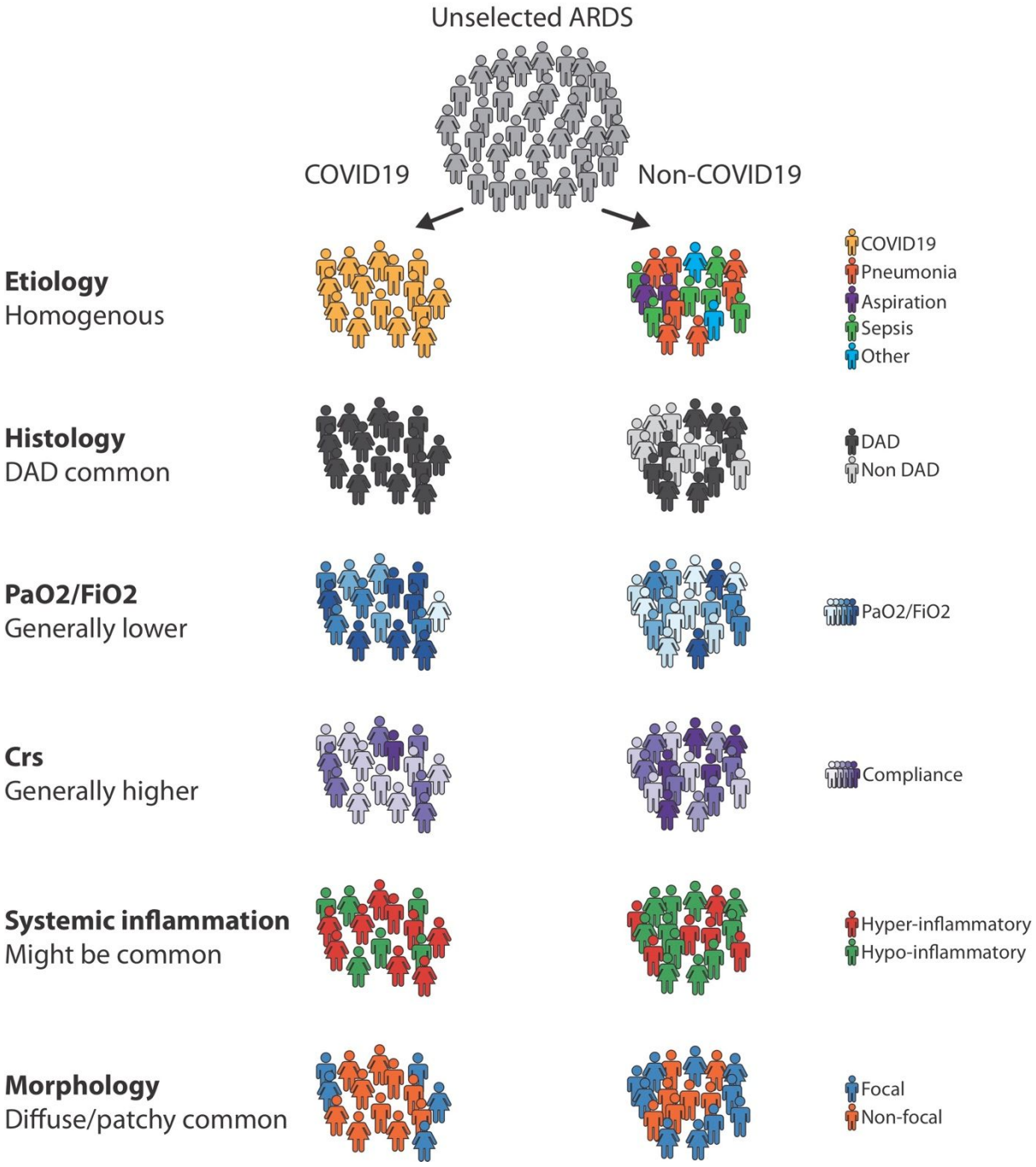
Figure 1: Subphenotypes of ARDS, stratified for the etiological subphenotype of COVID-19 related ARDS.



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COVID-19 Phenotypes and Potential Harm of Conventional Treatments: How to Prove the Hypothesis

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To the Editor:

Based on recent correspondence (1) and an expert editorial (2), two phenotypes of severe COVID-19 pneumonia have been proposed: *"**Type L**, characterized by **L**ow elastance (i.e., high compliance), **L**ow ventilation to perfusion ratio, **L**ow lung weight and **L**ow recruitability and **Type H**, characterized by **H**igh elastance, **H**igh right-to-left shunt, **H**igh lung weight and **H**igh recruitability."* (2)

Features of the L phenotype are not typical of ARDS as defined by the Berlin criteria. Importantly, the authors suggest recommended treatment strategies for severe COVID-19 pneumonia based on ARDS management (3) may lead to disease progression and excess harm. (1, 2) The authors provide anecdotal evidence for their observations based on their combined experience of treating several hundred severe COVID-19 cases. As outlined by Singer et al (4), we need a rational approach. Considering the potential importance for modifying the management of these patients and the growing volume of data available from China and Italy, quantitative data is needed to test this hypothesis. Balancing the trade-off between *"learning"* and *"doing"* in this pandemic is crucial. (5) Large randomised controlled trials are not yet available and observational data remains at high risk of bias. A number of predictive models have been described with severe methodological flaws. (6) The appropriate use of emerging observational data requires collaborative input to improve understanding of treatment effects and complement the results of ongoing randomised controlled studies.

The wealth of data generated by critically ill patients and the complexity of covariate interactions make it challenging to use traditional statistical modelling to establish causal relationships. We aim to determine the causal pathway between the use of an ARDS management strategy for 'L' phenotype patients and subsequent harm using a directed

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acyclic graph (DAG), Figure 1. The DAG achieves two things. Firstly, we can construct a complex system of interacting baseline, clinical and disease features allowing explicit statement of prior knowledge before any data analysis. Secondly, we can use the DAG to determine a minimal adjustment set of variables to reliably estimate the direct effect of our exposure (ARDS ventilation strategy in COVID-19 'L' phenotype patients) and outcome (ICU mortality).

The DAG was developed based on the information in the expert editorial outlining the two phenotypes. In doing so we have transformed the initial hypothetical construct into a testable mechanistic structure. Arrows represent proposed causal pathways such as the link between a high PEEP strategy of standard ARDS management and worsening oedema 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 AKI, all of which are readily measurable amongst 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 due to 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

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available on request). We would also be interested to know the calculated effects if anyone wishes to test the hypothesis with appropriately collected data.

Figure 1: Proposed directed acyclic graph.

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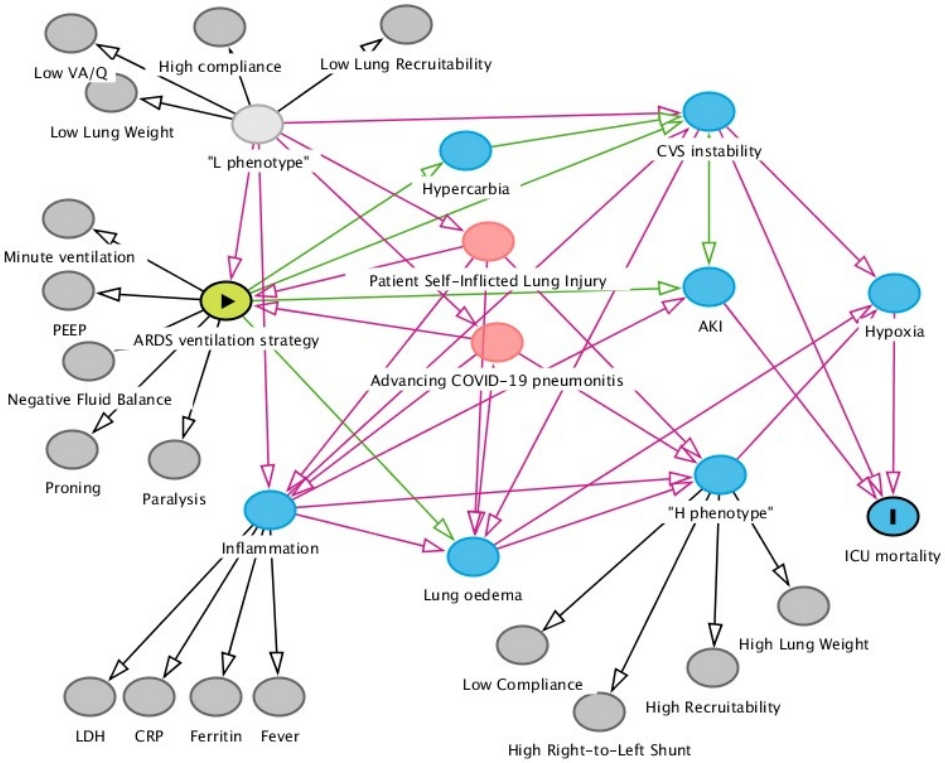

Proposed directed acyclic graph.

279x229mm (72 x 72 DPI)

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Severe Hypoxemia in Early COVID-19 Pneumonia

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To the Editor:

Luciano Gattinoni is widely acknowledged and respected for his work on ARDS, and this time he has suggested a very interesting concept describing the pathophysiology of the atypical presentation of 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 COVID-19 patients. The suggested cause of hypoxemia in Type L is the loss of regulation of perfusion and loss of hypoxic vasoconstriction. Hypoxemia, leading to increase minute ventilation, primarily by increasing the tidal volume (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 which may determine the transition from the Type L to the Type H phenotype. However, the authors did not give explanation for loss of regulation of perfusion and loss of hypoxic pulmonary vasoconstriction.

We believe that diffuse pulmonary micro vascular 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]

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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 type L patients. However, we have reservation on the "early intubation and the use of PEEP to prevent the transition to type H", as the authors themselves have suggested that "the lung conditions are too good". Effective oxygenation using HFNC/ECMO in type L should prevent pleural pressure swings and self-inflicted lung injury, leading to transition to type H. Additionally, some degree of "permissive hypoxemia"[4] may also be accepted in type L patients to avoid ergotrauma, caused during ventilating the compliant lungs.

However, other patients, who worsen to Type H due to cytokine storm, as the authors have suggested, should be treated as severe ARDS, including higher PEEP, if compatible with hemodynamics, prone positioning and extracorporeal support.

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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/cmH_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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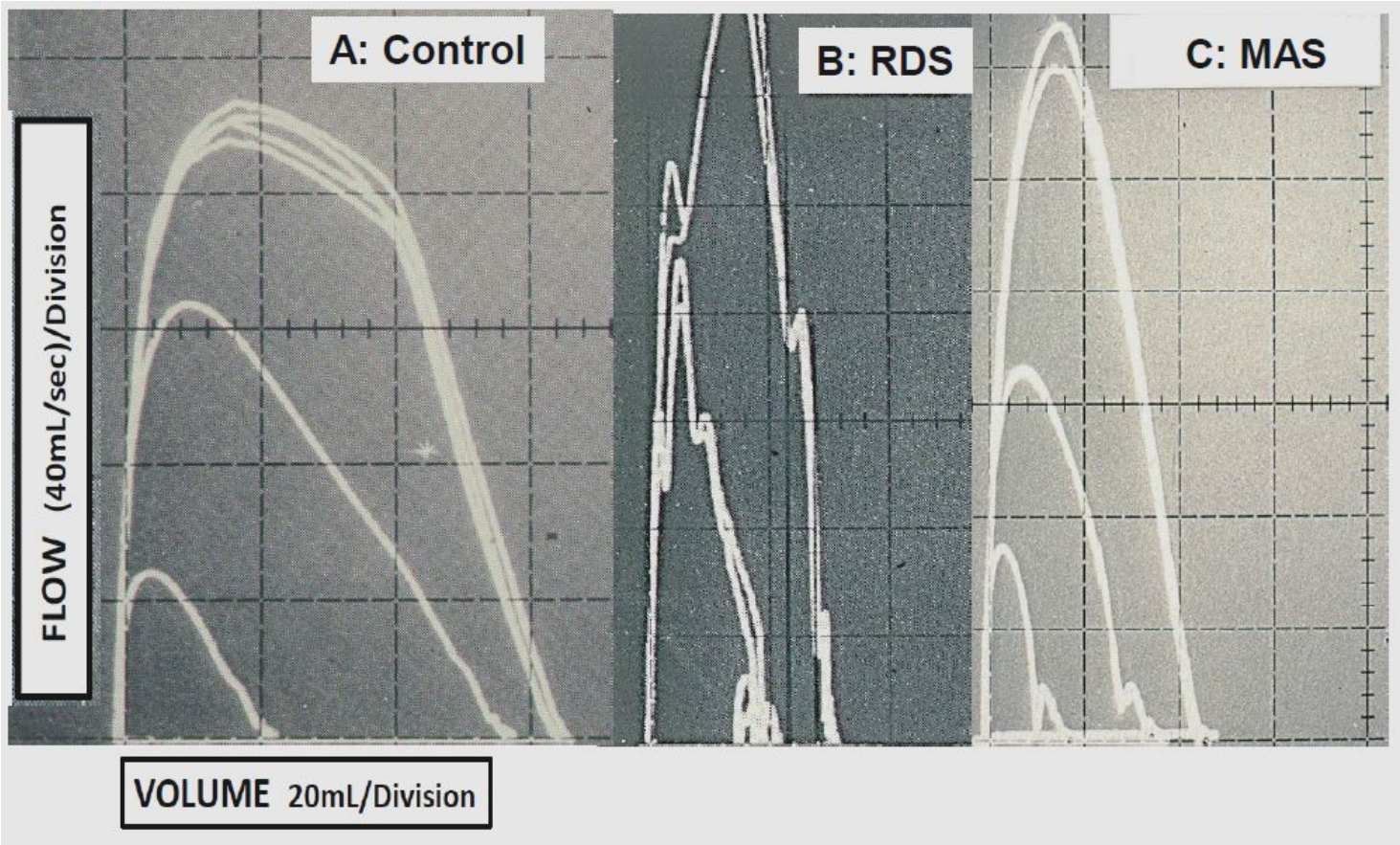
Figure 1.



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Heterogeneity of Acute Respiratory Distress Syndrome in COVID-19: "Typical" or Not?

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Dear Editor,

We read 'Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome' by Gattinoni and colleagues with great interest (1). In this letter, the authors describe 16 patients with COVID-19 who have a mean respiratory system compliance of 50.2 ± 14.3 ml/cmH2O and marked shunt physiology. The authors suggest that these patients are representative of the primary pattern of physiologic derangements among their patients and those of colleagues with whom they've conferred. They discourage the use of prone positioning when compliance is "relatively high," similar to their recommendations in a recent article in which they additionally support ventilation with tidal volumes up to 9ml/kg in select patients with COVID-19 and relatively preserved compliance (2). We appreciate the authors' clinical observations and their expertise, however we have several concerns with these two recommendations which diverge from the best established evidence for acute respiratory distress syndrome (ARDS).

First, the authors' reported cohort is small and heterogeneous, in keeping with the well-established heterogeneity of ARDS. Many of their patients have similar compliance to those enrolled in clinical trials for ARDS therapies (3). For reference, patients enrolled in the Prone Positioning in Severe ARDS (PROSEVA) trial had a mean respiratory system compliance of 35 ml/cmH_2O (standard deviation, 15) at the time of enrollment (3). Interestingly, a recent report of patients with COVID-19 from Seattle, Washington described median respiratory system compliance of 29 ml/cmH_2O (interquartile range, 25 to 36) (4). That is to say, 75% of the patients in the Seattle cohort had lung compliance of 36 ml/cmH_2O or less. The discrepancy between the compliance measurements in the cohorts from Gattinoni *et al* and Seattle

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highlights the difficulty in interpreting observations of small cohorts in a disease with well-established marked heterogeneity, such as ARDS (5).

Second, respiratory system compliance was not used to determine eligibility for prone positioning in past trials. The PROSEVA trial enrolled severely hypoxemic patients, meeting the Berlin criteria for ARDS, who failed to stabilize early in the course of management (3). While the authors may not support prone ventilation in patients with "relatively high compliance," exclusion of patients by these criteria would be inconsistent with existing evidence. Also, the effects of prone position on gas exchange are not limited to the shunt in fully atelectatic regions, but include changes in edematous regions. Discouraging prone position based on a perception of limited recruitability risks foregoing a therapy with mortality benefit (3).

Finally, progression to a classic ARDS with dense posterior consolidation and elevated critical opening pressures (recruitability) is well described following mechanical ventilation, even in patients with initially preserved mechanics and without established lung injury (6). Patients with COVID-19-associated respiratory failure have multifocal pneumonia even in milder stages and these regions are expected to have different elastic properties than unaffected tissue, causing regional stress and strain concentrations with potential to progress to severe ARDS (2, 4). Lung protective strategies, including low tidal volumes and prone positioning, exist to prevent this progression of lung injury.

We fully agree with the authors' final sentiment that patience and gentle ventilation are the best therapies for COVID-19 with associated ARDS. Further, the rapid search for new insights into COVID-19 is appropriate and commendable. However, adopting the paradigm that COVID-

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19 is inconsistent with ARDS, with resulting specific treatment recommendations, risks discouraging compliance with our best evidence-based standards of care. Evidence from randomized controlled trials suggests that prone positioning and low tidal volume ventilation are the precise strategies for gentle ventilation that patients with ARDS, “typical” or not, should receive.

Conflicts: Dr. Hardin reports research funding from AstraZeneca. Dr. Maley has no conflicts to report. Dr. Winkler has no conflicts to report.

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

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To the Editor,

The acute lung insult resulting from SARS-CoV-2 infection has multifarious clinical presentations ranging from limited mild respiratory symptoms to a potentially fatal multifocal pneumonia/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 this 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 re-analyzed 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 et al. (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/cmH2O (1), i.e. ~ 60% from normal. Based on these observations, the authors concluded that a relatively preserved compliance in Covid-19 pneumonia patients would make "high" PEEP ineffective, and thus unnecessarily dangerous, and make prone position worthless due to a low benefit/resource ratio. However, Crs values in this study were exceptionally variable, ranging from 20 to 90 ml/cmH2O. In other words, a significant reduction in Crs is present in intubated COVID patients, at least at some point during the evolution of the

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disease. Second, low Crs values averaging 35.7 ± 5.8 mL/cmH2O (in eight consecutive COVID patients studied at day 1 post-intubation) and 19.58 ± 7.96 mL/cmH2O (worst respiratory mechanics in 12 COVID patients) were reported by Liu et al. (2) and by Pan et al. (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 ARDS patients (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 et al. (3), and found a significant correlation between the level of PEEP used in their patients and Crs (Figure 1 A) – 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 cmH2O was used in a patient with a Crs of 12 ml/cmH2O, while another patient with a Crs of 30 ml/cmH2O was exposed to a PEEP of 15 cmH2O. In addition, since a significant increase in alveolar PCO_2 ($PACO_2$) was always present as low tidal volumes were used (3), we recomputed alveolar PO_2 (PAO_2) based on the data available (3). PAO_2 was calculated according to the alveolar gas equation, using $PaCO_2$ and FIO_2 provided (3) and the gradient PaO_2-PAO_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 PaO_2-PAO_2 gradient (Figure 1). This indicates that despite an unusual severity of hypoxemia in this population, a coupling between low compliance and high a-A 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

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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 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.

2- Does minimally increasing tidal volume improve pulmonary gas exchange or are the "COVID lungs" non-recruitable?

Lui et al. have shown that increasing V_T from 7 to 7.5 ml.kg produced a significant decrease in PaCO2 (2). We have reevaluated this question by determining the averaged dead space *ventilation* ($\dot{V}_D$) in patients receiving a tidal volume of 7 ml/kg (2). To do so, average alveolar ventilation ($\dot{V}_A$) was calculated from PaCO2 ($\dot{V}_A = k.\dot{V}_{CO2}/PaCO2$), then $\dot{V}_D$ was determined as minute ventilation (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 these given V_D, creating isoV_D -curves. As shown in figure 1, when V_T was increased from 7 to 7.5 ml/kg, the decrease in V_D/V_T ratio was much higher than expected from a mono-alveolar model (same isoV_D -curve), reflecting the recruitment of lung regions with high $\dot{V}A/Q$ ratio (lowering V_D). These data therefore suggest that at a low "cost" in terms of barotrauma, it is possible via

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a modest increase in tidal volume to reduce *serial dead space ventilation* (as expected) along with a decrease in *parallel dead space ventilation*.

The phenotype of patients in acute respiratory failure with" COVID lungs" is certainly quite heterogenous; individual determination of Crs, PA-aO_2 gradient and $PaCO_2$ as a function of the level of PEEP and tidal volume 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 along 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 to operate with the highest possible compliance and lowest PA-aO2 gradient in these patients.

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Figure Legend:

Figure 1. **A:** Values of Crs collected in mechanically ventilated COVID patients compared to data reported in ARDS (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 COVID and ARDS patients. **B**: Relationship between PEEP and CRS, showing that when low levels of PEEP were used, low Crs where always present (see text for comments and discussion). **C:** Crs vs PaO_2-PAO_2. Extreme deterioration of PaO_2-PAO_2 gradient was observed in many patients; yet, the patients with the lowest CRS have the greatest gradient, the correlation remains weak in this limited population. **D**: relationship between Crs/PEEP ratio vs PaO_2-PAO_2, 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**: IsoV_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 dead space (see text for further comments)

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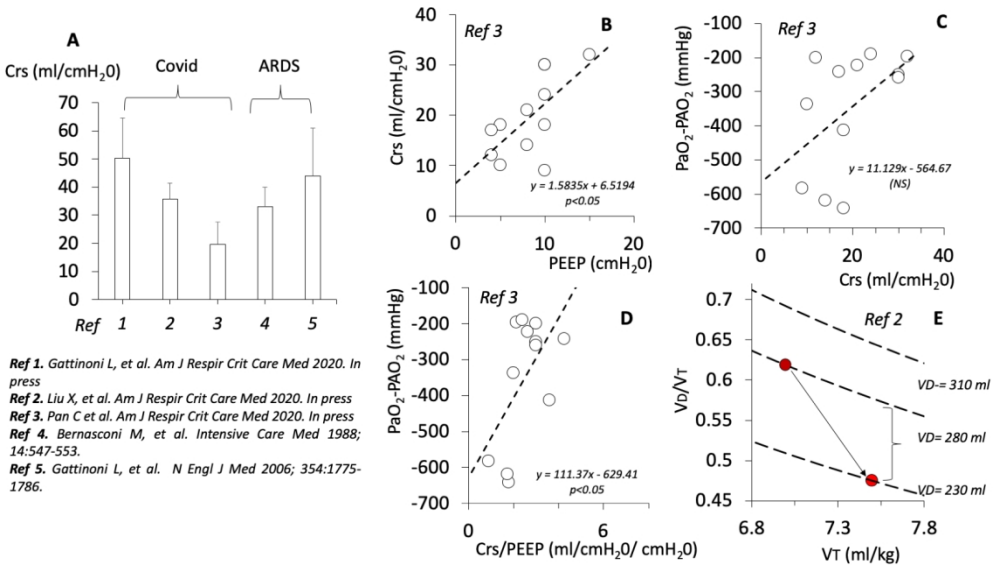

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Figure 1. A: Values of Crs collected in mechanically ventilated COVID patients compared to data reported in ARDS (the references of the selected studies are given in the figure). Although data were not obtained at the same time of the disease, alterations of the elastic properties of the respiratory system can be significant in all these patients and are not dramatically different between COVID and ARDS patients. B: Relationship between PEEP and CRS, showing that when low levels of PEEP were used, low Crs where always present (see text for comments and discussion). C: Crs vs PAO2-PaO2 gradient. Extreme deterioration of PAO2-PaO2 gradient was observed in many patients; yet, the patients with the lowest CRS have the greatest gradient, the correlation remains weak in this limited population. D: relationship between Crs/PEEP ratio vs PAO2-PaO2 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: IsoVD curves showing the relationship between VT and VD/VT ratio. By minimally increasing VT, the change in VD/VT ratio and thus in alveolar gas composition improves out of proportion of the changes in serial dead space (see text for further comments)

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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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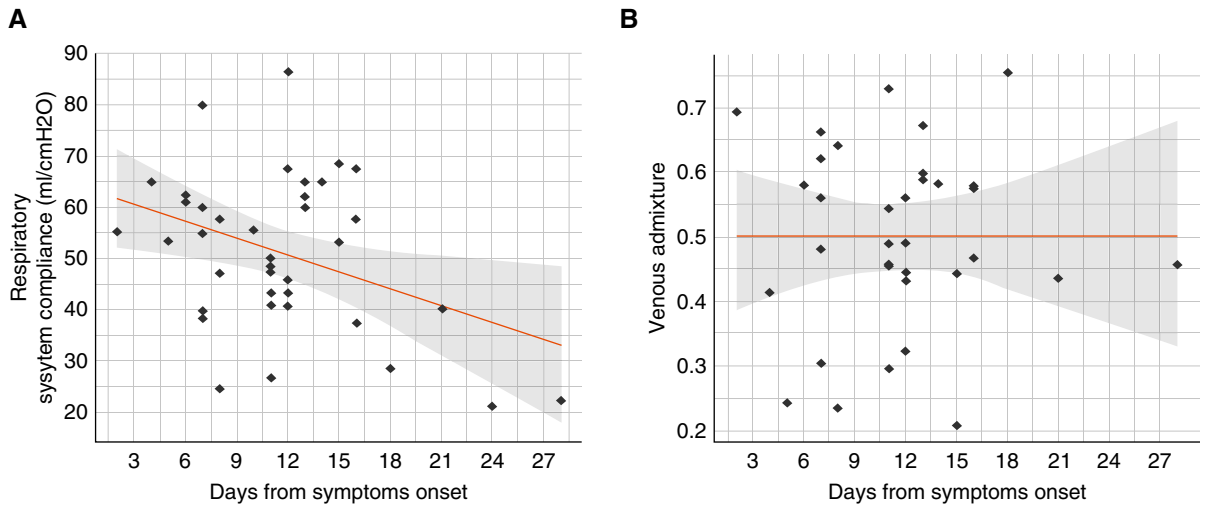

Figure 1. (*A*) Respiratory system compliance measured at 5 cm H_2O of positive end-expiratory pressure within 48 hours after admission to the ICU as a function of the days elapsed since the onset of symptoms ($P < 0.001$). (*B*) Venous admixture fraction (measured in the same conditions) as a function of the days elapsed since the onset of symptoms ($P = 0.964$).

preserved, the hypoxemia must primarily derive from the perfusion side (7). Indeed, a growing number of observations show endothelial involvement (8), which initiates hypercoagulability (9), and the lung perfusion dysregulation that causes severe hypoxemia because of $\dot{V}_A/\dot{Q}$ mismatch. However, as pointed out by Bhatia and Mohammed, microthrombosis are likely part of this phenomenon. In this context, Hedenstierna and colleagues suggested that inhaled nitric oxide could be of interest to correct hypoxemia. This is rational and certainly possible, but only further observations may tell us the value of inhaled nitric oxide in the different stages of the disease. Given that the hypoxemia is mainly determined by a pathology on the endothelial side of the alveolar membrane, the use of exogenous surfactant suggested by Koumbourlis and Motoyama lacks physiological rationale.

Thus, so far, we have learned that COVID-19 is a systemic disease in which the viral assault is primarily focused on the endothelium, which accounts for both the pulmonary vascular dysregulation and the hypercoagulable state. Are these insights sufficient to rethink and change our practice, and if so, at which stage? Fowler and colleagues, recognizing the difficulties of promptly organizing randomized controlled trials, propose a direct acyclic graph to evaluate the hypothetical risks and benefits of conventional therapies for the two extreme phenotypes. In the meantime, how should we manage type L patients? The transition from L to H status, in which the ARDS criteria and therapies fully apply, may be due both to the natural course of the disease and to the patient self-induced lung injury (10). There is little that can be done to alleviate the first factor, but we can certainly intervene to prevent patient self-induced lung injury. If, despite noninvasive support, the patient continues to make vigorous inspiratory efforts, we believe that mechanical ventilation should be applied without delay. During the mechanical ventilation of these early phase L patients, higher PEEP is not advisable despite the severe hypoxemia because recruitability is relatively low, the lung is already full of gas, and the consequences on hemodynamics may be remarkable. We also proposed in these L patients a V_T higher than 6 ml/kg, provoking a strong disagreement by Maley and colleagues, for whom the conventionally low V_T ventilation is the precise strategy for gentle lung ventilation. However, in those patients with higher Crs, the tradeoff is between possible ventilator-induced lung injury and possible hypoventilation, with an increased need for sedation and risk of atelectasis. We believe that in the L patients the risk of ventilator-induced lung injury is minimized, as plateau, driving pressure, and mechanical power are far from their conventionally accepted thresholds. In addition, we would like to respectfully remind our correspondents that in three large randomized controlled trials, no differences were found between patients treated with 7.1 ml/kg versus 10.3 ml/kg ideal body weight (IBW) (11), 7.2 ml/kg versus 10.8 ml/kg IBW (12), 7.3 ml/kg versus 10.2 ml/kg IBW (13).

ARDS is of fundamental importance in the ICU community, which developed in parallel to the understanding of the syndrome (14). Many people have argued that the term "ARDS" is too generic because it encompasses too many conditions and etiologies to have any credible diagnostic and prognostic validity. It is therefore ironic to see how many try to turn strongly in favor of preserving the diagnosis of ARDS in COVID-19 disease, particularly because COVID-19 is a single-etiology disease (unlike ARDS), and the ventilatory management is independent from the degree of hypoxemia (unlike ARDS). Standard ARDS treatment in such cases should be deeply reconsidered, taking also in account that the mortality rate in different ICUs around the world ranges from 10% to 90% (personal communications). Because the disease is the same, this disparity underlines the impact of treatment. ■

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

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Reply by Pan *et al.* to Haouzi *et al.*

From the Authors:

We appreciate Dr. Haouzi and his colleagues for their interest in our research letter (1). They reanalyzed our reported data and found a possible but nonsignificant coupling between lower compliance and greater alveolar P_{O_2} ($P_{A_{O_2}}$)–Pa_{O_2} gradient. They then suggested that positive end-expiratory pressure (PEEP) should be titrated by reaching the highest compliance and lowest $P_{A_{O_2}}$–Pa_{O_2} gradient.

We want to point out that a possible association between compliance and $P_{A_{O_2}}$–Pa_{O_2} gradient among different patients makes physiological sense but may not be applied for PEEP titration in a given individual; the PEEP providing the highest compliance can be completely different from the PEEP providing the lowest $P_{A_{O_2}}$–Pa_{O_2} gradient. Actually, we have observed that patients with coronavirus disease (COVID-19)–associated acute respiratory distress syndrome (ARDS) from Wuhan often present "better" compliance and "worse" $P_{A_{O_2}}$–Pa_{O_2} gradient at low PEEP. We thus will discuss the optimal compliance and the optimal $P_{A_{O_2}}$–Pa_{O_2} gradient as two respective PEEP strategies.

Titrating PEEP by the optimal compliance has been proposed for several decades, but years of research have shown many pitfalls and limitations. *1*) Plateau pressure can be measured by performing varied durations of end-inspiratory occlusion, and the pressure value can change according to viscoelastic properties, pendelluft, or simply the presence of leaks. This technical issue is not trivial. A preset 0.2- to 0.3-second end-inspiratory pause minimizes this issue, providing more reliable plateau pressure as an indicator of the maximal lung distension (2). *2*) Some physiological studies using electrical-impedance tomography suggested that a high PEEP guided by "best" compliance of the whole respiratory system can be substantially higher than the PEEP based on regional compliance or on the dorsal fraction of ventilation reaching 50% and that the chest wall could play a role in these discrepancies (3). *3*) In contrast, when substantial tidal recruitment is present at low PEEP, compliance may be increased by this tidal recruitment (4). Using this "best" compliance would therefore favor ongoing repeated recruitment and collapse. *4*) The optimal compliance approach has been tested in a large randomized controlled trial, showing no benefit on outcome (5).

The $P_{A_{O_2}}$–Pa_{O_2} gradient can be a useful physiological indicator during clinical practice, but we cannot rely on it for PEEP titration because of the following considerations. *1*) Calculating the

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