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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

Originally Published in Press as DOI: 10.1164/rccm.202004-1052LE on June 24, 2020

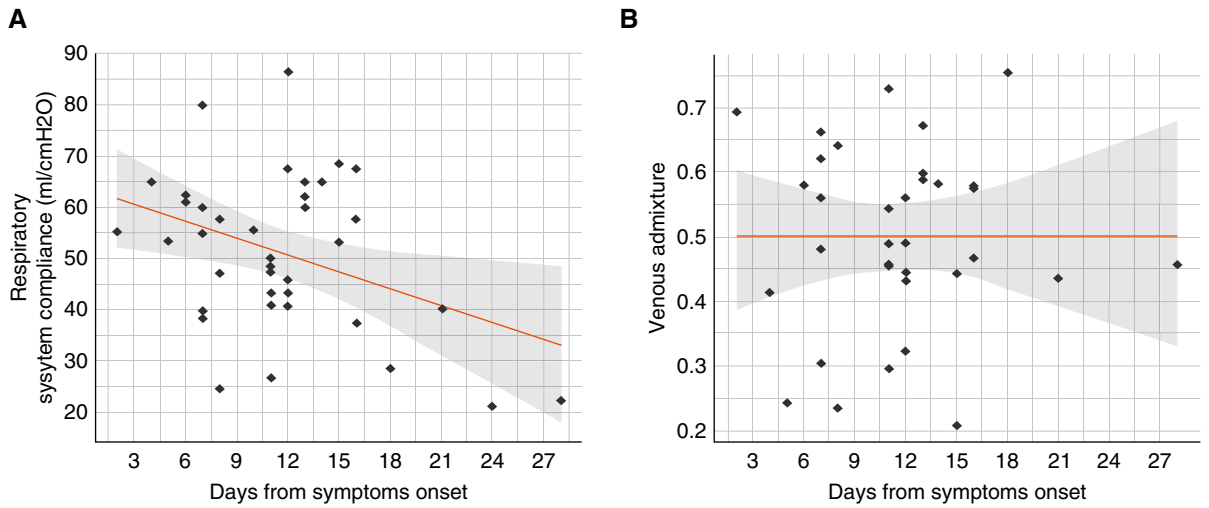

Figure 1. (*A*) Respiratory system compliance measured at 5 cm H_2O of positive end-expiratory pressure within 48 hours after admission to the ICU as a function of the days elapsed since the onset of symptoms ($P < 0.001$). (*B*) Venous admixture fraction (measured in the same conditions) as a function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

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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

Originally Published in Press as DOI: 10.1164/rccm.202005-2045LE on June 24, 2020