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.

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