"Established" Respiratory Treatment in Acute Respiratory Distress Syndrome: Scientific Rigor or a Square Peg in a Round Hole?

To the Editor:

Dr. Hardin, in his editorial (1), surmises that there is nothing new under the sun, particularly that established ventilatory approaches should also be applied to coronavirus disease (COVID-19) acute respiratory distress syndrome (ARDS) (C-ARDS). We know of only two trials in unselected (“average”) ARDS that provide significant results: one establishing that 6 ml/kg is better than 12 ml/kg and the other establishing that positive end-expiratory pressure (PEEP) higher than 15 cm H2O increases mortality. Further advances in ARDS treatment were only proved or suggested in subgroups: prone position if PaO2/FIO2 ratio is below 150 mm Hg and higher PEEP in hyperinflammatory phenotypes. Therefore, subgroups deviate from the average ARDS behavior and require modification of standard management.

Like many, we are not so certain that all patients benefit from 6 ml/kg predicted body weight VT—ora tolerate the suggested entries of a PEEP–FiO2 table. Outcomes from intermediate VT may be, on average, equivalent to a lower VT (2). Many clinicians seem to have already figured this out; VT in all groups of the Panwar study (3) was set in the 7–8 ml/kg range, which is similar to those in the quoted article by Hager and colleagues (4).

Lung protection is linked to repetitive excessive “strain”; consequently, VT is ideally set individually in relation to gas volume or compliance (i.e., driving pressure) rather than predicted body weight. In patients with relatively preserved lung gas volumes (e.g., many with early-stage COVID-19), very low VTs may lead to dyspnea or asynchronies, adversely affecting the outcome. Conversely, even VT of 6 ml/kg may be excessive for some patients with very severe ARDS. In this context, it does not seem a paradox that in LUNG-SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure), patients with better compliance had a larger VT, from 6 ml/kg predicted body weight VT to 8 ml/kg range, which is similar to those in the quoted article by Hager and colleagues (4).

Established respiratory treatment in acute respiratory distress syndrome (ARDS) (C-ARDS) is a heterogeneous syndrome. Given this heterogeneity, there have been many efforts to define subgroups of patients with ARDS: by etiology, by respiratory mechanics, by the distribution of radiographic abnormalities, by the severity of gas exchange abnormality, or by biomarkers. In their reply to the editorial "Novel Phenotypes in Respiratory Failure: Same as It Ever Was" (1), Dr. Camporota, Dr. Gattinoni, and Dr. Marini articulate the plausible and widely held hypothesis that such subgroups would benefit from distinct treatment strategies. Indeed, this hypothesis has animated much of the recent research literature on ARDS. To date, however, it has proven surprisingly difficult to prospectively demonstrate a mortality benefit from any particular tailored approach. Prone ventilation has proven...
beneficial for patients with a PaO₂/FiO₂ (P/F) ratio < 150, though many clinicians continue to harbor suspicion that those are not the only patients who benefit. In contrast, trials that enrolled patients regardless of subtype have shown robust mortality benefits. Although studies are urgently needed to examine the hypothesis that Camporota and colleagues articulate, plausibility and internal consistency of a hypothesis are not the standards on which we should base a change in practice. In the particular case of coronavirus disease (COVID-19), we have witnessed the widespread adoption of plausible therapies that subsequently proved to be of no benefit (2). For the present, the best evidence indicates that patients with acute onset of respiratory failure that is not fully explained by fluid overload, bilateral infiltrates, and P/F ratio < 300 on positive-end expiratory pressure (PEEP) of at least 5 cm H₂O benefit from low Vt ventilation, regardless of etiology.

I agree wholeheartedly with the letter writers that lung strain—increment from resting volume—is likely the key mechanical determinant of lung injury in ventilated patients with ARDS. I further agree that Vt alone is a poor proxy for lung strain. There have been signals of this in the literature, notably the retrospective study demonstrating a stronger association of driving pressure with mortality than of Vt (3). It is therefore plausible that there exists a better way to determine what strain is tolerable in a given patient. Absent of evidence, however, we must not become overly persuaded by the plausibility of any given hypothesis. After all, it is very plausible that there exists a way to titrate PEEP to an individual patient’s mechanics, and yet, thus far, trials have consistently failed to demonstrate a benefit to individualized PEEP titration.

With respect to their assertion that ARDS secondary to COVID-19 presents with a distinct distribution of respiratory system compliance, the authors are on less solid ground. In support, they cite an editorial by Dr. Marini, which was published in association with an electrical impedance tomography study of 10 patients in a single center. In contrast, the now multiple large case series of patients with COVID-19 (4, 5) report distributions of respiratory system compliance (and P/F ratio) that are remarkably consistent with large case series before the COVID-19 pandemic, such as LUNG-SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) (6). The literature to date simply does not support the idea that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a mechanically distinct form of respiratory failure.

While we await further investigation and potential identification of individualized therapies that improve outcomes, clinicians should feel very comfortable with the continued application of the evidence-based therapies developed in the era before COVID-19.

References

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Are Ground-Glass Opacities on Chest High-Resolution Computed Tomography a Manifestation of Airway Disease?

To the Editor:

We commend the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana del Tórax for the publication of the first hypersensitivity pneumonitis (HP) clinical practice guidelines (1). The guidelines propose two distinctive subtypes of HP: nonfibrotic and fibrotic, as determined by the presence of radiological and/or histopathological fibrosis.

In their Table 5, the authors propose that a “nonfibrotic typical HP pattern” on chest computed tomography (CT) requires the identification of at least one feature of lung infiltration—mosaic attenuation or ground-glass opacities (GGOs)—plus at least one abnormality indicative of small airway disease—ill-defined centrilobular nodules or air trapping.

However, as the authors pointed out, mosaic attenuation per se is not specific for lung infiltration, because in diseases that affect both the lung parenchyma and the small airways (e.g., HP), mosaic attenuation can be due to either GGOs or air trapping and the difference is established by expiratory CT images (1).

Therefore, to be more specific and to avoid confusion, would it not be better to use either GGOs or mosaic attenuation due to GGOs as the sole criterion for lung infiltration on Table 5, because they represent the same phenomenon?

On the other hand, in their Table 6, the authors propose that a “fibrotic typical HP” pattern on CT requires the identification of at least one feature of lung fibrosis in a specific distribution, and at least one abnormality indicative of small airway disease: ill-defined centrilobular nodules and/or GGOs, or mosaic attenuation.