

EDITORIAL



# What have we learned ventilating COVID-19 patients?

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The spectrum of coronavirus disease 19 (COVID-19) ranges from asymptomatic to mild respiratory disease, pneumonia, acute respiratory distress syndrome (ARDS), multiorgan failure, and death. About 5% of COVID-19 patients require ICU admission and ~3.5% develop ARDS, although this number depends on reporting bias, practice patterns, and resource availability. In this Editorial, we present a viewpoint on the ventilatory management of COVID-19-induced ARDS, based on the underlying pathophysiology. Our message is simple: after almost a year of treating ARDS caused by COVID-19, everything—and nothing—has changed [1].

## Pathophysiology of COVID-19 ARDS

The angiotensin-converting enzyme 2 (ACE2) receptor is the functional SARS-CoV-2 receptor, and along with the transmembrane serine protease 2 (TMPRSS2) is required for viral entry into cells [2]. The ubiquity of this receptor can explain many manifestations of COVID-19. The lung is a prime target for SARS-CoV-2 because of its huge surface area which is in direct contact with the inspired air (and possible SARS-CoV-2 virions), and the expression of ACE2 in surfactant-producing alveolar type-II cells. Infection of the latter likely explains the atelectasis and pneumonia observed in COVID-19 patients. ACE2 expression in many cell types can also explain other organ involvement in COVID-19 (e.g., heart, kidney, blood vessels, skin), and perhaps some of the more unique findings including anosmia (olfactory support cells) and “happy hypoxemia” (carotid body).

The available pathological findings of COVID-19 ARDS suggest diffuse alveolar damage along with pulmonary vasculature involvement [3], which have been recognized as important features of ARDS for decades. Widespread pulmonary macro/microthrombi are commonly found in autopsies of patients with ARDS from any etiology at any phase of the disease. The biggest controversy is whether the pathophysiology of COVID-19 ARDS is different from non-COVID-19 (classical) ARDS. A number of editorials, opinion pieces, and small reports have suggested that COVID-19 ARDS is atypical, since some patients with severe hypoxemia had relatively normal respiratory compliance, with implications for ventilatory management [4, 5]. However, the heterogeneity of classical ARDS is well documented, and alterations of gas-exchange and respiratory system compliance in COVID-19 ARDS [6–8] appear comparable to, and within the range of values reported for classical ARDS [9], including in a case series published in 2006 [10]. Some of the differences found may be due to differences in setting PEEP, reinforcing the need to individualize PEEP, as opposed to using a “one-size-fits-all” approach [11].

## Ventilatory management

Although some patients with COVID-19 can be managed with supplemental oxygen and non-invasive ventilation, patients with severe respiratory failure require endotracheal intubation and invasive mechanical ventilation. Some authors have recommended early intubation to avoid the risk of patient self-induced lung injury [4, 5], or that measurement of “esophageal pressure swings is crucial” to decide when to intubate [5]. However, a paucity of data exists to justify this approach, and there are very compelling reasons to oppose a policy of early intubation [12]. Until more data are available on this issue, we recommend using similar criteria regarding intubation that are used for classical ARDS [11].

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There is significant variability in ventilatory practice when treating patients with ARDS. Since, as discussed above, COVID-19 ARDS is similar to classical ARDS, the foundations of ventilatory management should also be similar: provide lung protective ventilation [11]. Although there is no unique recipe on how best to ventilate an ARDS patient, protective ventilation with low tidal volumes (4–8 mL/kg predicted body weight), plateau pressures < 30 cmH<sub>2</sub>O and driving pressures < 15 cmH<sub>2</sub>O, is strongly associated with improved outcomes in ARDS patients. Patients with moderate-to-severe ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> ratio < 150 mmHg) should be ventilated in the prone position unless there are contraindications. Prone positioning reduces the pleural pressure gradient and leads to more uniform distribution of ventilation and lung strain, usually leading to an improvement in oxygenation and, most importantly, decreasing ventilator-induced lung injury. It has been suggested that prone positioning should be minimized in COVID-19 ARDS patients with higher compliances, based on the argument that the putative different respiratory physiology makes prone ventilation unlikely to be beneficial [5]. However, although there is great heterogeneity, COVID-19 ARDS patients appear to have similar recruitability [7]. The oxygenation response to prone positioning appears similar to non-COVID-19 ARDS: Ziehr et al. found that PaO<sub>2</sub>/FiO<sub>2</sub> increased from a median of 150 mmHg in the supine position to 232 mmHg in the prone position [13].

### Extracorporeal membrane oxygenation (ECMO)

Early in the pandemic, a number of small case reports suggested that mortality of patients treated with ECMO was > 90%. However, recent studies suggest that COVID-19 patients placed on ECMO have reasonable outcomes. In a series of 83 patients with severe COVID-19 ARDS treated with ECMO, estimated 60-day mortality (31%) was similar to previous studies of severe classical ARDS [14]. A recent study using the Extracorporeal Life Support Organization (ELSO) Registry examined the outcomes of 1035 COVID-19 patients who received ECMO [15]. In the subset of patients with ARDS ( $n=799$ ), the vast majority of whom received vvECMO, the cumulative 90-day hospital mortality was 38%, a figure similar to the 35% 60-day mortality in the EOLIA trial [16]. As with virtually all studies, in COVID-19 there was an increased mortality with increasing age. These data suggest that vvECMO is a viable therapy in COVID-19 patients with very severe ARDS, and for now it seems reasonable to use EOLIA inclusion criteria to identify suitable candidates in centers experienced with the use of ECMO.

### Concluding remarks

COVID-19 ARDS is ARDS, a syndrome which, notwithstanding the significant heterogeneity, has been amenable to significant improvements in its management. In the same vein, subphenotypes should be properly defined and management changes should be clearly demonstrated [17]; everything else is speculation. Recent studies demonstrating that corticosteroids decrease mortality in ventilated COVID-19 patients are an excellent example of validating proposed management changes [18]. Although the data are still limited and we have much to learn in this ongoing pandemic, we have enough evidence at this point to recommend that the ventilatory management of patients with COVID-19 ARDS should be similar to other causes of ARDS, tailored to the specific patient.

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#### Author contributions

UT, ASS, and JV wrote the final version of the manuscript. All authors contributed to the revision, and read and approved the final version of the manuscript.

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#### Conflicts of interest

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