COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted?

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The COVID-19 pandemic has seen a surge of patients with acute respiratory distress syndrome (ARDS) in intensive care units across the globe. As experience of managing patients with COVID-19-associated ARDS has grown, so too have efforts to classify patients according to respiratory system mechanics, with a view to optimising ventilatory management. Personalised lung-protective mechanical ventilation reduces mortality and has become the mainstay of treatment in ARDS. In this Viewpoint, we address ventilatory strategies in the context of recent discussions on phenotypic heterogeneity in patients with COVID-19-associated ARDS. Although early reports suggested that COVID-19-associated ARDS has distinctive features that set it apart from historical ARDS, emerging evidence indicates that the respiratory system mechanics of patients with ARDS, with or without COVID-19, are broadly similar. In the absence of evidence to support a shift away from the current paradigm of ventilatory management, we strongly recommend adherence to evidence-based management, informed by bedside physiology, as resources permit.

Introduction

The global experience of managing patients with COVID-19-associated acute respiratory distress syndrome (ARDS) is rapidly expanding, along with an increasing number of reports on respiratory system mechanics and ventilatory management.[1–6] Over the past two decades, the heterogeneity of ARDS has increasingly been recognised, and efforts have been made to describe subgroups of patients with different clinical and biological characteristics, clinical outcomes, and treatment responses.[7,8] As hospitals have faced a surge of patients with COVID-19 and health-care professionals have worked under enormous pressure, often with limited resources, to save the lives of patients with ARDS, observations of heterogeneity in both the clinical features and clinical course of COVID-19-associated ARDS have led to proposals for different management strategies on the basis of described phenotypes.[9–11] Phenotypic heterogeneity is an important concept, but there is a risk of overinterpretation or inappropriate application of these principles, which can have detrimental implications for outcomes of ventilatory management. Given the importance of lung-protective mechanical ventilation in ARDS, in this Viewpoint we address ventilatory strategies in the context of recent reports that discussed phenotypic heterogeneity in patients with COVID-19-associated ARDS.[9–11] Without a strong evidence base to guide a shift from the current paradigm of patient management, we strongly recommend adherence to evidence-based management,[12] informed by bedside physiology, and supported by current data.

Key messages

- During an outbreak such as the COVID-19 pandemic, it is important to balance the rapidly evolving and initially low-level evidence—largely case series, case reports, and anecdotes—with the scientific rigour needed to support any necessary shifts in the current paradigm of patient management
- The notion that acute respiratory distress syndrome (ARDS) is a heterogeneous syndrome is a ubiquitous finding as old as the concept of ARDS itself, contributing substantially to the complexity of its management; heterogeneity is most relevant when linked to differential treatment effects, which have been shown to improve outcomes
- Reports of phenotypic heterogeneity in patients with COVID-19-associated ARDS, although interesting, could easily be overinterpreted or inappropriately applied in the intensive care unit, potentially leading to detrimental ventilatory management strategies in these patients
- Large observational studies suggest that patients with COVID-19-associated ARDS have similar respiratory system mechanics to patients with ARDS from other causes and that, for most patients, COVID-19-associated ARDS is, in the end, ARDS
- We strongly recommend adherence to evidence-based management, informed by bedside physiology, and supported by outcome data; this approach includes lung-protective mechanical ventilation, individualised positive end-expiratory pressure, prone positioning, and venovenous extracorporeal membrane oxygenation—as suggested by international guidelines for ARDS, and as resources permit

Description of phenotypes in COVID-19-associated ARDS

In a case series of 16 mechanically ventilated patients with COVID-19, Gattinoni and colleagues[9] described severe hypoxaemia despite relatively normal lung compliance—an unusual finding in patients with severe ARDS. In eight patients, blood gases and CT scans revealed a large shunt fraction despite relatively small amounts of gasless tissue, suggesting hyperperfusion of poorly ventilated lung regions. Because the lungs appeared relatively open, they recommended a lower positive end-expiratory pressure (PEEP) strategy, as well as avoidance of prone positioning, especially because of potential limitations in human resources during the pandemic.

In a second report,[10] the authors highlighted the non-uniformity of patients with COVID-19-associated ARDS and proposed the existence of two primary phenotypes: type L (low values of elastance, pulmonary ventilation/perfusion ratio, lung weight, and recruitability) and type H (high values of elastance, right-to-left shunt, lung weight, and recruitability), with the latter being more consistent with what they describe as typical severe ARDS. Gattinoni and colleagues proposed that most patients present early with type L, and that some transition to type H, potentially

due to the synergistic effects of worsening COVID-19 pneumonia and patient self-inflicted lung injury.[13] Therefore, the authors[10] advocated early endotracheal intubation in patients with excessive inspiratory efforts, and stated that once "…deeply sedated, the Type L patients, if hypercapnic, can be ventilated with volumes greater than 6 mL/kg (up to 8–9 mL/kg) predicted body weight, as the high compliance results in tolerable strain without the risk of VILI [ventilator-induced lung injury]".[10] A third report on this subject re-emphasised these key points.[11]

We are at an early stage in understanding the heterogeneity of COVID-19-associated ARDS (eg, pathophysiological features, clinical course, biomarkers, and phenotypes based on respiratory mechanics). The rigorous identification of phenotypes could ultimately help to guide the management of patients who are critically ill with COVID-19. At present, we argue that an evidence-based approach informed by decades of research in ARDS is needed.

Recommendations for management of COVID-19-associated ARDS

The notion that ARDS is a heterogeneous syndrome—presenting with variable mechanical and gas exchange disturbances—is an important but ubiquitous finding and as old as the concept of ARDS itself. This clinical and biological heterogeneity contributes substantially to the complexity of managing the syndrome. Heterogeneity is clinically relevant when linked to differential treatment effects. For example, hyperinflammatory versus hypoinflammatory subphenotypes might respond differently to PEEP levels and fluid management.[14,15] Identifying recruitability with a simple bedside technique could help to tailor ventilatory management in patients with ARDS, including those with COVID-19.[1,16] However, the application of such a tailored physiological approach does not necessarily equate to improved outcomes with that treatment. Similarly, an atypical presentation of ARDS does not necessarily mean that the patient will respond differently to a typical treatment regimen.[3]

In this context, we propose recommendations for the treatment of COVID-19-associated ARDS, from both a practical and theoretical perspective. First, lung protection with volume-limited and pressure-limited ventilation was initially shown to be effective in a heterogeneous ARDS population with a wide range of physiological parameters, including static compliance, plateau pressure, and the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen[17] Similar to patients with COVID-19 with the proposed L phenotype, patients with mild ARDS typically have higher respiratory system compliance than do those with more severe ARDS. Some data suggest that a lung-protective strategy can be beneficial even in patients with relatively low plateau pressures.[18] Moreover, a number of studies have shown that using lung-protective ventilation in patients who have relatively normal lungs is associated with fewer pulmonary complications, including decreased progression to ARDS, and improved clinical outcomes.[19] Patients with the robust inflammatory response common in COVID-19 are probably biologically primed to develop ventilation-induced lung injury.[20] The respiratory system mechanics and risk of lung strain in these patients might worsen quickly, especially with the resumption of spontaneous efforts to breathe.[21] Therefore, liberalising tidal volumes in these patients might be associated with worse outcomes, even if they do not have what might be regarded as typical ARDS.

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	Italy[9]	Seattle, WA, USA[33]	Italy[34]	Boston, MA, USA[2]	Amsterdam[3]	New York City, NY, USA[5]	New York City, NY, USA[4]
Number of patients	16	24	1300	66	38	257	267
Respiratory support*							
Invasive mechanical ventilation	16 (100%)	18 (75%)	1150 (88%)	66 (100%)	38 (100%)	203 (79%)	267 (100%)
Non-invasive ventilation	0	0	137 (11%)	1 (2%)	0	3 (1%)	51 (19%)
HFNC	0	10 (42%)	0	1 (2%)	0	12 (5%)	0
PaO_2/FiO_2 ratio	..	142 (94–177)	160 (114–220)	182 (135–245)	132 (48)†	129 (80–203)	103 (82–134)
Compliance, mL/cm H_2O	50 (14·3)†	29 (25–36)	..	35 (30–43)	49 (24)†	26 (21–38)	28 (23–38)
Plateau pressure, cm H_2O	..	25 (20–28)	..	21 (19–26)	21 (7–23)	27 (22–31)	25 (21–29)
PEEP, cm H_2O	..	..	14 (12–16)	10 (8–12)	10 (9–12)	15 (12–18)	10 (8–12)
Tidal volume, mL/kg PBW	..	..	..	..	..	6·2 (5·9–7·2)	7·0 (6·1–8·1)
FiO_2	..	90% (70–100)	70% (50–80)	..	..	100% (80–100)	..
Prone positioning	Not reported	5/18‡ (28%)	240/875§ (27%)	31 (47%)	Not reported	35 (17%)	108 (40%)
ECMO	Not reported	0	5/498§ (1%)	3 (5%)	Not reported	7 (3%)	Not reported

Data are n (%) or median (IQR), unless otherwise indicated. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. HFNC=high-flow nasal cannula. PaO_2=partial pressure of arterial oxygen. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure. *Some patients received more than one type of respiratory support. †Mean (SD). ‡Denominator is 18 for the group that had invasive mechanical ventilation. §It is not explicitly stated in the manuscript why the denominators are different, although they might represent the group of patients for which these data were collected and available at the time of analysis.

Table 1: **Selected ventilatory characteristics of critically ill patients with COVID-19**

	Considerations	Potential course of action
Timing of intubation	• No high-quality clinical trial evidence addressing optimal timing of intubation in ARDS is available • Intubation might be beneficial in patients with high respiratory drive and at high risk of patient self-inflicted lung injury[13] • Non-invasive ventilation has been associated with worse outcomes when PaO_2/FiO_2 ratio <150 in ARDS[39] • Detrimental consequences of intubation and invasive ventilation (eg, related to sedation, paralysis, and endotracheal tube complications) might outweigh benefits, especially in patients with mild hypoxaemia and without high respiratory drive or work of breathing; consequences for other patients because of bed and ventilator shortages in the ICU should be considered	• Consider timely intubation as indicated by refractory hypoxaemia or hypercapnia, and by objective evidence of high work of breathing on clinical examination (eg, phasic [not tonic] contraction on palpation of sternomastoid)[40] or by oesophageal manometry[41]
Tidal volume	• Low tidal volume ventilation results in improved outcomes in patients with and without ARDS and should be the starting point for ventilatory management of patients with ARDS (ie, 6 mL/kg PBW)	• Lower tidal volume as needed to 4 mL/kg PBW to keep plateau pressure <30 cm H_2O[37] • Liberalise tidal volume (up to 8 mL/kg PBW) in patients who are double triggering, or if inspiratory airway pressure decreases below PEEP, keeping plateau pressure <30 cm H_2O[36] • Ideally, keep driving pressure ≤14 cm H_2O[42]
PEEP	• Higher PEEP might be beneficial in patients with high recruitability, with better gas exchange and reduced risk of ventilator-induced lung injury • Higher PEEP can be harmful in patients with low recruitability, who have hypoxaemia due largely to pulmonary vascular pathology; high PEEP can lead to adverse haemodynamic effects or barotrauma • Improvement in partial pressure of arterial oxygen with increased PEEP can be misleading	• Individualise PEEP;[28] consider higher PEEP in patients with evidence of higher potential for recruitment (eg, as suggested by CT scan or recruitment to inflation index[16]) or with a body habitus or clinical exam that suggests high pleural pressures are likely • Evaluate response to changes in PEEP at the bedside[43]
Prone positioning	• Prone positioning is associated with improved outcomes in patients with moderate or severe ARDS, with improved ventilation or perfusion matching, more homogeneous distribution of ventilation, and reduced risk of ventilator-induced lung injury[44] • Staffing and resource demands can limit feasibility during surges in case volume • Efficacy and safety of prone positioning in awake, non-intubated patients remain unclear[45–47] and are being evaluated in clinical trials in patients with COVID-19 (NCT04350723, NCT04347941, NCT04365959)	• In the absence of contraindications, use prone positioning in mechanically ventilated patients with PaO_2/FiO_2 ratio <150[48]
Venovenous ECMO	• Patients can develop refractory hypoxaemia or have mechanics leading to potentially injurious levels of mechanical ventilation, despite optimisation of conventional measures • Staffing and resource demands can limit feasibility during an increase in the number of cases	• Consider venovenous ECMO in patients with refractory hypoxaemia or high driving pressures or respiratory acidosis despite conventional lung-protective measures (eg, higher PEEP or prone positioning)[49]

ARDS=acute respiratory distress syndrome. ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. ICU=intensive care unit. PaO_2=partial pressure of arterial oxygen. PBW=predicted bodyweight. PEEP=positive end-expiratory pressure.

Table 2: **Clinical and physiological considerations in the management of patients with COVID-19-associated ARDS**

Gattinoni and colleagues[10] recommended the use of tidal volumes greater than 6 mL/kg predicted bodyweight for patients with type L COVID-19-associated ARDS who develop hypercapnia. Because of the potential for greater ventilator-induced lung injury with higher tidal volumes, we suggest that clinicians first address common treatable causes of hypercapnia before resorting to the use of higher tidal volumes. These causes might include the following: inadequate respiratory rate; increased dead space from a heat and moisture exchange filter at the Y-connector,[22] which might be used out of an abundance of caution to prevent cross-contamination, instead of a heated humidifier; or ventilators used without the circuit compliance compensation turned on, reducing the volumes delivered to patients.[23] Meticulous attention to these details, before consideration of abnormal vascular components of dead space as a cause of hypercapnia, is strongly encouraged before increasing the tidal volume above 6 mL/kg predicted bodyweight.

Second, what level of hypercapnia is tolerable? Permitting hypercapnia with the use of lower tidal volumes might mitigate the initial risk of ventilator-induced lung injury and be well tolerated. But it is also associated with a number of detrimental effects such as: facilitating bacterial growth in the lung; inhibiting alveolar wound repair, reabsorption of alveolar fluid, and alveolar cell proliferation; and increasing pulmonary hypertension.[24] The acceptable degree of hypercapnia in a patient will depend in part on any associated metabolic acidosis or haemodynamic instability.[25]

Third, the proposed temporal evolution of the type L and type H subtypes, in contrast to previous reports in patients with ARDS,[26] raises the important question of whether the proposed subtypes merely reflect the natural evolution of ARDS. This issue is particularly relevant in patients with COVID-19-associated ARDS who might have been intubated earlier in the disease course than is usually the case. Comparison of data between reports is difficult because the decision to intubate might have been made at distinctly different timepoints in the course of patients' illness at different centres due to resource limitations. All of this raises the difficult question of the optimal point at which to intubate a given patient, because we know that the window can be narrow and that the consequences of intubating too early or too late could be substantial.[27]

Fourth, the question of what PEEP levels to use is more complex than the previous discussion on the management of tidal volume. Previous data already suggest that the same PEEP should not be applied to all patients with ARDS;[28] individualisation is needed because the response to PEEP differs on the basis of individual respiratory mechanics. The seminal studies of Suter and colleagues[29] and Dantzker and colleagues[30] showed that PEEP can improve hypoxaemia while reducing tissue oxygen delivery. If, in fact, there is a subphenotype in which vascular derangement is the major mechanism for the hypoxaemia (eg, loss of pulmonary vasoconstriction, or pulmonary emboli or thrombi), then increasing PEEP might not improve hypoxaemia. Therefore, PEEP should be targeted to improve oxygen delivery while mitigating the risk of ventilator-induced lung injury and patient self-inflicted lung injury, depending on the clinical context. This titration remains complicated to achieve in patients with ARDS with or without COVID-19.

Evidence for phenotypes in COVID-19-associated ARDS

Nearly a third of patients in the reports by Gattinoni and colleagues[9,10] had severe (proposed type H) ARDS, consistent with previously reported patients with ARDS.[31,32] In two reports of patients receiving mechanical ventilation for COVID-19-associated ARDS from New York City, NY, USA,[4,5] the median respiratory system compliances were 28 mL/cm H_2O and 26 mL/cm H_2O, not unusual for patients with ARDS. Similar values of compliance were reported in two smaller studies from Seattle, WA, USA[33] and Boston, MA, USA[2] (median compliances of 29 mL/cm H_2O and 35 mL/cm H_2O, respectively; table 1). These data do not preclude the existence of subphenotypes with high respiratory system compliance. However, they do suggest that, on average, patients with COVID-19-associated ARDS probably have similar respiratory system mechanics to patients with ARDS from other causes and that, for most patients, COVID-19-associated ARDS is, in the end, ARDS.[35] Viewing COVID-19-associated ARDS as a different entity suggests the need to abandon current treatment principles in favour of a new approach. Without robust evidence to the contrary, a new approach should not be considered because of risks of harm. Patients with moderate-to-severe COVID-19-associated ARDS should receive prone positioning and patients with severe ARDS might need venovenous extracorporeal membrane oxygenation, as indicated in international guidelines for ARDS,[36–38] and as resources permit.

Conclusions and future directions

What does all of this mean for how we should ventilate patients with ARDS due to COVID-19? Table 2 outlines our recommendations to help set ventilatory strategy based on underlying pulmonary pathophysiology in patients with COVID-19. We suggest that the focus should be on using our existing ARDS ventilation evidence base to guide therapy,[36–38] while adjusting as necessary based on individual patient-specific issues. For example, apparent heterogeneity might be due to the fact that there is a distinct underlying pathological process contributing to hypoxaemia in some patients, which requires non-ventilatory therapy (eg, increased prevalence of thrombo-embolic complications in COVID-19).[50] Of course, if such a patient requires mechanical ventilation, it is not appropriate to use a ventilatory strategy that largely targets fluid-filled, atelectatic lungs. Clinicians should adapt their management plan to each patient, accounting for their individual characteristics, as well as their preferences and values—the advice is not a one-size-fits-all approach.

In the midst of a pandemic, we can serve our patients best by organising and participating in collaborative research programmes to facilitate learning while caring for patients, to better inform the management of critically ill patients with COVID-19.[51,52] Particularly in this era of social media, we need to balance anecdotes and case reports[53] with the scientific rigour needed to support any necessary shifts in the current paradigm of patient management.[54] Until such new data emerge, we should continue to manage patients with ARDS from COVID-19 pneumonia with our current evidence-based practices,[7] informed by bedside physiology.

Search strategy and selection criteria

We searched PubMed for articles published in English between Jan 1, 1950, and June 8, 2020, using combinations of the terms "coronavirus", "COVID-19", "SARS-CoV-2", "nCoV", "acute respiratory distress syndrome", "mechanical ventilation", "critical care", and "intensive care". We determined which articles were relevant on the basis of the article's title and citations. We also found articles through searches of the authors' personal files and reviewed relevant references cited in retrieved articles. The final reference list was generated on the basis of relevance to the topics covered in this Viewpoint.

Contributors

EF and DB conceived the manuscript. EF conducted the search and drafted the manuscript. All authors critically revised the manuscript and accepted the final version for publication.

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