



Protective ventilation in patients with acute respiratory distress syndrome related to COVID-19: always, sometimes or never?

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Purpose of review

To review current evidence on the pathophysiology of COVID-19-related acute respiratory distress syndrome (ARDS) and on the implementation of lung protective ventilation.

Recent findings

Although multiple observations and physiological studies seem to show a different pathophysiological behaviour in COVID-19-ARDS compared with 'classical' ARDS, numerous studies on thousands of patients do not confirm these findings and COVID-19-ARDS indeed shares similar characteristics and interindividual heterogeneity with ARDS from other causes. Although still scarce, present evidence on the application of lung protective ventilation in COVID-19-ARDS shows that it is indeed consistently applied in ICUs worldwide with a possible signal towards better survival at least in one study. The levels of positive end-expiratory pressure (PEEP) usually applied in these patients are higher than in 'classical' ARDS, proposing once again the issue of PEEP personalization in hypoxemic patients. In the absence of robust evidence, careful evaluation of the patient is needed, and empiric settings should be oriented towards lower levels of PEEP.

Summary

According to the present evidence, a lung protective strategy based on low tidal volume and plateau pressures is indicated in COVID-19-ARDS as in ARDS from other causes; however, there are still uncertainties on the appropriate levels of PEEP.

Keywords

acute respiratory distress syndrome, coronavirus disease 2019, lung protective ventilation, mechanical ventilation

INTRODUCTION

Before answering the question whether and when lung protective ventilation should be applied to patients with acute respiratory distress syndrome due to coronavirus disease-19 (COVID-19-ARDS), it is useful to briefly recall why this question is so relevant both from a clinical and a research standpoint.

As the first cases of COVID-19 began to emerge in early 2020, it became clear that the consistent observation of bilateral interstitial pneumonia and severe hypoxemia allowed to classify the most severe cases of COVID-19 as having ARDS [1*]. However, in a matter of weeks, clinical observations and expert opinions began to emerge, suggesting that COVID-19-ARDS was in fact a different form of ARDS [2]. Most of these conclusions were based on the observation that COVID-19 patients showed 'abnormally high' levels of static compliance and lung volumes and

'abnormally low' oxygenation parameters, not totally justified by the amount of nonventilated parenchyma on computed tomography (CT) scan [3].

These doubts, which are still partially unsolved, led many to the conclusion that 'atypical' ARDS does not need 'typical' lung protective ventilation [4]. A wide debate among experts in the field followed and fuelled a number of important studies

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KEY POINTS

- COVID-19-ARDS shares most of its pathophysiological hallmarks with ARDS from other causes.
- Lung protective ventilation (tidal volume 6 ml/kg and plateau pressure <30 cmH₂O) is widely applied in COVID-19-ARDS.
- PEEP titration, as in ARDS from other causes, may be challenging and requires careful monitoring.
- Lower levels of PEEP may be appropriate, at least in patients with higher levels of static respiratory system compliance and/or dead space.

[5[■],6,7[■],8–10] that we will review in the second part of this article. Before that, however, we shall briefly review the state of the art of lung protective ventilation in ARDS.

Lung protective mechanical ventilation in acute respiratory distress syndrome

Mechanical ventilation is a lifesaving technique in several forms of acute respiratory failure. At the same time, extensive studies have demonstrated that the inappropriate application of mechanical ventilation can worsen/induce lung injury (so-called ‘ventilator induced lung injury’ (VILI)) [11–14].

The main ‘classical’ determinants of VILI are barotrauma and volutrauma, that occur because of high volumes or pressures [14]; atelectrauma and biotrauma occur at lower lung volumes by the cyclic opening and closing of lung units [14]. More recently, the ‘unifying’ concept of ergotrauma (damage because of excessive mechanical energy) has been developed and the mechanical power has been proposed as a single variable encompassing all the factors involved in VILI development [15].

Increasing understanding of the mechanisms behind VILI has led to the development of the concept of protective mechanical ventilation. The two main aspects of protective mechanical ventilation are to limit tidal volume (V_T) and plateau pressures to prevent lung damage caused by overdistension [13] and to set the appropriate positive end-expiratory pressure (PEEP) level to minimize the cyclic opening and closing of airways and lung units [16].

The landmark ARMA trial has shown significant mortality reduction when a protective ventilatory strategy of V_T 6 ml/kg predicted body weight (PBW) and plateau pressure less than 30 cmH₂O was used compared with traditional ventilatory setting [13], and this strategy is still strongly recommended in adult patients with ARDS [17,18]. More recently,

airway driving pressure (ΔP) has been shown to be a strong predictor of mortality even in patients receiving ‘protective’ plateau pressures and V_T [19]. In fact, at least from a physiological standpoint, driving pressure is a more precise way of normalizing tidal volume to the size of the ARDS lung (surrogated by respiratory system compliance) [18].

The main concern about setting PEEP remains the selection of its optimum level that can simultaneously minimize VILI, improve oxygenation with no hemodynamics effects. In fact, excessive PEEP levels to counteract atelectrauma may lead to excessive lung parenchymal strain and finally to barotrauma, which could be worse than atelectrauma itself [20]. An individual meta-analysis summed up results of three RCTs that studied the effect of high vs. low PEEP level [21–23] and showed no statistical difference in overall hospital mortality but a relative mortality reduction in moderate and severe ARDS patients when a high PEEP level strategy was used [16]. These results suggest that adult patients with moderate or severe ARDS may benefit from higher rather than lower levels of PEEP [17]. However, a more recent trial applying a strategy of high PEEP combined with aggressive recruitment maneuvers (targeted at obtaining an ‘open lung’) showed increased mortality compared with a more conservative protective strategy with relatively high incidence of barotrauma [24]. Moreover, several methods and approaches for estimating lung recruitability (and consequently guide PEEP titration) have been proposed in the last three decades based on respiratory system mechanics [19], transpulmonary pressure measurements [25,26], CT-scan analysis [27], electrical impedance tomography [28,29] and others [13,21] but none of those provided compelling evidence of superiority [18,30] as the individual response to PEEP is highly variable.

All these controversial results lead many to doubt on whether an open lung should be the target of a protective ventilatory strategy in ARDS [31]. Moreover, the notion that PEEP could be increasing the energy load delivered to the lung in the theoretical framework of ergotrauma, further supports the hypothesis that tolerating at least small amounts of ‘closed’ (or cyclically opening–closing) lung can be less dangerous than barotrauma and volutrauma because of high levels of distending pressure [20,31,32].

Coronavirus disease 2019-acute respiratory distress syndrome: similarities and differences from ‘classical’ acute respiratory distress syndrome

As briefly stated in the introduction, bilateral infiltrates developing less than a week from COVID-19

onset, accompanied by oxygenation deficit with $\text{PaO}_2/\text{FiO}_2$ ratio 300 mmHg or less are common in COVID-19 patients with pneumonia; consequently, these patients can be classified as having ARDS, according to the Berlin definition [33]. The incidence of ARDS in more than 2000 hospitalized COVID-19 patients was reported to be ~30%, with a mortality rate ~45% [34]. Although initial case series reported much higher mortality rate in mechanically ventilated patients compared with ARDS from other causes, recent data reported a 28-day mortality consistent with classical ARDS, ranging between 15 and 50% [34]. Decreasing in mortality rate from the early pandemic to current days may be due mostly to organizational factors and the initial overwhelming pressure on limited healthcare resources [35].

Soon after the pandemics began, physiologic data underlining the heterogeneity of COVID-19-ARDS patients began to emerge [2–4]. In particular, the presence of severe hypoxemia often associated with near normal respiratory system compliance seemed to suggest the presence of two distinct phenotypes of COVID-19-ARDS: one, supposed to be more common during the early stage of COVID-19 disease (type L), characterized by lower elastance, ventilation to perfusion (VA/Q) ratio, lung weight and recruitability; the other phenotype (type H) was characterized by higher elastance, right-to-left shunt because of more nonaerated tissue for increased edema and high lung weight and lung recruitability, similar to classical ARDS [3]. These two phenotypes were also supposed to be the expression of different phases of the same disease. Thus, patients with type L may evolve into type H phenotypes for disease progression because of viral replication and the worsening pneumonia or to patient self-inflicted lung injury. Type H patients were suggested to be treated as classical severe ARDS, including lung protective ventilation strategies, higher PEEP, prone positioning, and extracorporeal supports. When mechanical ventilation is required in type L, same authors suggested lower levels of PEEP because of low recruitability and possible detrimental hemodynamic effects; ventilation with volumes greater than 6 ml/kg was also proposed (up to 8–9 ml/kg) [3].

These early observations incited conduction and publication of several studies, investigating differences and similarities between classical ARDS and COVID-19-ARDS. The focus was especially pointed at static compliance and its possible use for patient phenotyping and consequent clinical management. The tendency to higher compliance with median values higher than 40 ml/cmH₂O was shown by some studies [5[•],7^{••},9] but not confirmed in several other studies, where compliance was lower and

similar to classical ARDS [6,8,10,36,37]. Interestingly, in the study by Grasselli *et al.*, although showing higher median values of static compliance, only 6% of patients with COVID-19-associated ARDS had compliances greater than the 95th percentile of the classical ARDS cohort [5[•]]. The wide range of static compliance reported in literature becomes narrower in studies with more than 100 patients, and the inclusion of higher numbers of patients seems to be associated to a lower tendency to differ from classical ARDS.

Furthermore, a recent secondary analysis of the LUNG SAFE study investigated the distribution of compliance phenotypes in classical ARDS and their relationship with mortality. Among more than 1000 patients included in the analysis, more than 10% had preserved compliance (>50 ml/cmH₂O) with a significant lower mortality compared with patients with lower compliance (<40 ml/cmH₂O) (32 vs. 45%); moderate and severe hypoxemia were also found in a significant proportion of patients with relatively high static compliance [38^{••}]. We can conclude that respiratory static compliance is a heterogeneous parameter either in COVID-19 or classical ARDS. An important additional finding is the absence of correlation between respiratory static compliance and $\text{PaO}_2/\text{FiO}_2$ ratio, especially in COVID-19-ARDS [5[•]].

Different mechanisms may play a role in causing severe hypoxemia in COVID-19 patients, such as intravascular disorder. During SARS-CoV-2 infection, one of the most reported alteration is a hypercoagulability state with high incidence of disseminated intravascular coagulation, pulmonary intravascular coagulation, venous thromboembolism, pulmonary embolism and arterial thrombosis [39]. In a cohort physiologic study performed on 10 patients affected by COVID-19 related ARDS, Mauri and colleagues showed an elevated ventilation/perfusion mismatch, with larger prevalence of ventilated non perfused lung units (dead space) compared with perfused non-ventilated units (shunts). This report suggested a larger dead space and increased pulmonary vessel resistance caused by micro–macro thrombosis [40^{••}]. Serum concentration of D-dimer is an independent risk of mortality, and, whenever combined with static respiratory compliance evaluation may enhance the prediction of mortality in COVID-19 patients [5[•],41].

Other authors proposed the classification into two phenotypic subgroups of COVID-19-ARDS based on demographic, respiratory and laboratory data including markers of coagulopathy (D-dimer, PT and aPTT) and end-organ dysfunction (decreased pH, increased lactate, creatinine and troponin-T). A minority of patients (27%), included in the group (class 2) with increased organ dysfunction

Table 1. Characteristics and outcomes of patients with classical acute respiratory distress syndrome and coronavirus disease 2019-acute respiratory distress syndrome in observational studies

	Classical ARDS			COVID 19-ARDS		
	Berlin definition physiologic database (n = 269) [33]	LUNG SAFE (n = 2377) [38 ^{***} ,45]	Grasselli <i>et al.</i> (n = 301) [5 [*]]	Ferrando <i>et al.</i> (n = 742) [8]	Botta <i>et al.</i> (n = 553) [6]	Chiumello <i>et al.</i> (n = 32) [7 ^{***}]
Crs (ml/cmH ₂ O)	38 ± 15.2	34.7 ± 21.1	41 (33–52)	35 (27–45)	31.9 (26–39.9)	49.9 ± 15.4
PaO ₂ /FiO ₂ ratio	162 ± 57.1	161 (158–163)	124 (89–164)	120 (83–177)	158.8 (128.6–200.5)	106.5 ± 59.6
PEEP (cmH ₂ O)	11.5 ± 3.4	8.4 (8.3–8.6)	13 (10–15)	12 (11–14)	14 (11–15)	–
V _T /PBW (ml/kg)	–	7.6 (7.5–7.7)	7 (6.3–7.6)	6.9 (6.3–7.8)	6.3 (5.7–7.1)	7.7 ± 0.9
Pplat (cmH ₂ O)	–	23.2 (22.6–23.7)	24 (22–26)	25 (22–29)	–	17.2 ± 3.8
28-day mortality (%)	37	34.8	36	32	35	37.5
Ventilator-free days at day 28	8.5 (0–23.5) ^a 0 (0–16.5) ^b 0 (0–6.5) ^c	10 (0–22)	–	4 (0–18)	0 (0–15)	–
Ventilatory ratio (units)	–	–	1.76 (1.42–2.14)	2 (1.49–2.63)	–	1.76 ± 0.45
Total lung weight (g)	1466 (1213–1816)	–	1676 (1375–1876)	–	–	1596 ± 385

Data are presented either as mean ± SD or as median (IQR). Crs, static compliance of the respiratory system; PaO₂/FiO₂, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; V_T, tidal volume.

^aMild ARDS.

^bModerate ARDS.

^cSevere ARDS.

(prevalently renal and cardiac abnormalities), relative lactic acidosis and increased coagulopathy, showed an almost doubled 28-day mortality compared with class 1 (40 vs. 23.3%) [42].

All in all, the data we presented leads us to underline following points: patients with COVID-19-ARDS are clinically heterogeneous as the patients with ARDS from other causes (this is not surprising as ARDS is a syndrome and not a disease) [43]; lung mechanics and gas exchange appear to be comparable between COVID-19-ARDS and ARDS because of other causes [44]; COVID-19-ARDS patients are possibly characterized by more widespread vascular and thrombotic involvement than patients with classical ARDS (although thrombotic manifestations in these patients are known since the 1980s) [5^{*}].

Table 1 presents relevant respiratory and outcome variables in patients with ‘classical’ ARDS and COVID-19-ARDS in important observational studies [5^{*},6,7^{***},8,33,38^{***},45].

Lung protective ventilation in coronavirus disease 2019-acute respiratory distress syndrome patients

We should now integrate the elements of the previous paragraphs with the evidence on lung protective strategies in COVID-19-ARDS patients and consequently try to answer the question whether ‘classical’ lung protective ventilation is indicated in these patients. Unfortunately, specific evidence to date is still scarce and does not allow for definite conclusions. Many

other strategies already used in moderate-to-severe ARDS, such as prone positioning, muscle relaxation, nitric oxide and extracorporeal membrane oxygenation have been implemented in COVID-19-ARDS but are outside the scope of this review.

In a recent cohort study on 1503 critically ill COVID-19 patients conducted in Brazil, use of protective ventilatory settings (defined as tidal volume ≤8 ml/kg PBW and plateau pressure ≤30 cmH₂O) during the first 24 h of the ICU stay was associated (in a Cox proportional hazards model adjusted for compliance, PaO₂/FiO₂ ratio, PEEP and pH) with a statistically significant benefit in 28-day mortality (aHR 0.73, 95% CI 0.57–0.94). Moreover, nonsurvivors had slightly (but significantly) higher mean plateau pressure and driving pressure, compared with nonsurvivors (23 vs. 22 cmH₂O and 13 vs. 12 cmH₂O, respectively), while median PEEP was 10 cmH₂O both in survivors and nonsurvivors. By analyzing static compliance distribution, the authors could not show any bimodal distribution that could possibly lead to identification of phenotypes [46].

In a multicenter, retrospective observational study performed in 18 ICUs in the Netherlands on a total of 553 patients, Botta and coworkers showed that lung protective ventilation (in terms of low tidal volume and plateau pressure) was applied regularly on most COVID-19-ARDS patients, while PEEP setting was less consistent, with wider variability and a high median level of ~14 cmH₂O. However, although increasing tidal volume (normalized by PBW) was significantly associated with worse

outcome, PEEP was not, and the authors conclude that their data do not support the suggestion that there are distinct phenotypes needing different approaches in the titration of PEEP [6].

A scoping review of mechanical ventilation use in critically ill COVID-19 patients showed that, among more than 14 000 mechanically ventilated COVID-19 patients, the settings used for mechanical ventilation were relatively consistent across studies and generally followed usual recommendation for lung protective ventilation: median plateau pressures ranged between 20.5 and 31 cmH₂O, median driving pressures between 9.5 and 15 cmH₂O and set tidal volume rarely exceeded 7.5 ml/kg PBW [47]. However, median PEEP level was almost always at least 10 cmH₂O, a value substantially higher than recorded in the LUNG SAFE study [45].

A recent consensus statement using the Delphi method among 39 experts in the field shows wide agreement on the fact that COVID-19-ARDS is clinically similar to other forms of ARDS. A strong recommendation is to use lung protective ventilation (considered as tidal volume 4–6 ml/kg PBW, plateau pressure \leq 30 cmH₂O and driving pressure \leq 15 cmH₂O strong statement), while there was neither agreement for higher vs. lower PEEP strategy nor the method of PEEP selection in these patients [48].

The Surviving Sepsis Campaign Guidelines on the Management of Adults With COVID-19 in the ICU, even in their 2021 update continue to recommend a strategy of ventilation based on low tidal volume (4–8 ml/kg PBW), low plateau pressure ($<$ 30 cmH₂O) and higher PEEP ($>$ 10 cmH₂O), although they underline the need for close patient monitoring in order to avoid barotrauma [49,50].

As for classical ARDS, we think that there are more doubts than certainties on the correct setting of PEEP [31] and personalization according to physiologic measurements is of paramount importance. Nevertheless, current knowledge seems to point in the direction of caution in the use of higher PEEP strategies in these patients for at least two reasons. First, hyperinflation is a common occurring phenomenon both in classical ARDS [51] and in COVID-19-ARDS [5[■]], and there is growing evidence of increased alveolar dead space [5[■],7[■]] and limited recruitability in COVID-19-ARDS [52[■]]. Second, there is a worryingly high incidence of barotrauma and gas leak manifestations (pneumothorax and pneumomediastinum) in COVID-19-ARDS patients [53,54], which is probably because of specific characteristics of the lung parenchyma (so-called ‘lung frailty’) [55].

Nevertheless, we think that the principle of limiting tidal volume and distending pressure is still undisputed, even in the time of COVID-19; however, we could not insist too much in stressing the

importance of measuring relevant physiological variables (such as transpulmonary pressure and mechanical power) whenever possible and continuously re-evaluate the patient for obtaining the best possible ventilatory settings. Although we begin to understand more on the pathophysiology of COVID-19-ARDS and of other forms of ARDS, researchers and clinicians need to keep a ‘watchful eye’ and continue to explore the field, keeping in mind that there is probably not a single therapy for such a complex and heterogeneous syndrome.

CONCLUSION

With few exceptions, COVID-19-ARDS patients should be ventilated with usual lung protective settings, constituting low tidal volumes (6 ml/kg PBW), plateau pressures lower than 30 cmH₂O (always considering the wide variations in the resulting transpulmonary pressure), airway driving pressures lower than 15 cmH₂O and mechanical power possibly lower than 16 J/min. PEEP selection, as in classical ARDS, is the most challenging decision and requires careful evaluation of the patient; we suggest using lower PEEP levels whenever possible.

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Conflicts of interest

There are no conflicts of interest.

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