ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 12, Issue, 09, pp. 58736-58741, September, 2022
https://doi.org/10.37118/ijdr.24880.09.2022

REVIEW ARTICLE OPEN ACCESS

COVID-19-ASSOCIATED ACUTE RESPIRATORY DISTRESS SYNDROME: VENTILATOR MANAGEMENT AND PRONE VENTILATION

Umesh Kumar Bylappa*, Seddiqa Abdulrahim Al Mansoori, Sriharha Tatineni, Jacob Philip and Natasha Espinosa

Department of Respiratory Therapy, Sheikh Khalifa Medical City, Abu Dhabi, UAE

ARTICLE INFO

Article History:
Received 18th July, 2022
Received in revised form
27th July, 2022
Accepted 29th August, 2022
Published online 23rd September, 2022

Key Words:
ARDS, CARDS, ALI, VILI, P-SILI, PEEP, RCTs, Prone Ventilation, Lung Recruitment, V/Q Ratio, ECMO.

Corresponding author:
Umesh Kumar Bylappa

ABSTRACT

The COVID-19 associated acute respiratory distress syndrome (ARDS) is a major cause of acute respiratory failure. Its development leads to high rates of mortality, as well as short- and long-term complications, such as physical and cognitive impairment. Key components of a strategy include avoiding lung overdistension by limiting tidal volumes and airway pressures, and the use of positive end expiratory pressure with or without lung recruitment manoeuvres in patients with severe ARDS. In this review article, we describe updated concepts in ARDS and ventilator management for phenotypes: L and H type of Covid-19 ARDS patients. Specifically, its risk factors and pathophysiology, and current evidence regarding ventilation management, prone ventilation, and intervention required in refractory hypoxemia.

Citation: ***Umesh Kumar Bylappa, Seddiqa Abdulrahim Al Mansoori, Sriharha Tatineni, Jacob Philip and Natasha Espinosa.*** "Covid-19-associated acute respiratory distress syndrome: ventilator management and prone ventilation*", International Journal of Development Research*, 12, (09), 58736-58741.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS-CoV-2), is a single-stranded ribonucleic acid encapsulated corona virus and is highly contagious. Transmission is thought to be predominantly by droplet spread and direct contact with the patient, rather than 'airborne spread'. There is still no specific antiviral treatment for COVID-19 infection, only supportive therapies including respiratory care for affected patients, especially in more severe cases[1]. Approximately 15% of individuals with COVID-19 develop moderate to severe disease and require intensive care surveillance and ventilatory support, with a further 5% who require supportive therapies including intubation and ventilation. Current recommendations suggest early intubation of COVID19 patients mainly for two reasons: (A) severe hypoxemia with PaO2/FiO2 often <200mmHg, fulfilling Berlin criteria of moderate-to-severe acute respiratory distress syndrome (ARDS); and (B) to protect staff from viral transmission.2,3 Mortality during mechanical ventilation appears to be high, however, and lung protective ventilation is mandatory. The most common complication in severe COVID-19 patients is severe pneumonia, but other complications may include Acute Respiratory Distress Syndrome (ARDS), Sepsis and Septic Shock, Multiple Organ Failure, including Acute Kidney Injury and Cardiac Injury, which are more prevalent in at-risk groups including Older Age (> 60 years) and those with Co-morbid Diseases such as Cardiovascular Disease, Lung Disease, Diabetes and those who are Immunosuppressed.

Description of phenotypes in COVID-19 associated ARDS: In typical ARDS, there is a reasonably good relationship between the degree of hypoxemia and the shrinking baby lung such that as oxygenation worsens, strain, stress and calculated elastance are all also high [i.e. compliance falls]. With these abnormal mechanics, patients often breathe with a shallow pattern to minimize the elastic work, but rapidly to maintain carbon dioxide excretion. A rapid-but-shallow breathing pattern itself can cause dead space and energetic failure of the respiratory pump. COVID-19 ARDS is not typical ARDS! There is a mismatch between the severity of hypoxemia and the calculated elastance. There is preserved elastance because the resting lung volume is close to normal and therefore lung strain and stress are near-normal. Thus, patients are less disposed to rapid-shallow-breathe and may have less energetic demand placed upon the respiratory pump. CT evidence supports these findings: the early CARDS lung is seen to have low elastance, low lung weight, low response to positive end-expiratory pressure – hence the term 'L' type CARDS. The hypoxemia appears to be primarily a vascular event: the lungs have lost their protective ability to pinch off

perfusion to areas of compromised gas exchange. If COVID-associated ARDS progresses, the peripheral ground glass and interstitial edema which typify the L-type can morph into a typical ARDS pattern with dependent consolidations and 'baby lung' physiology. Then, the patient is observed to have high elastance [stiff lungs], high lung weight and high response to PEEP – hence the term 'H' type (Table-1).

COVID-19 pneumonia- L Type: At the beginning COVID-19 pneumonia presents with following characteristics:

Low elastance: The nearly normal compliance indicates that the amount of gas in the lung is nearly normal.[4]

Low ventilation-to-perfusion (VA/Q) ratio: Since the gas volume is nearly normal, hypoxemia may be best explained by the loss of regulation of perfusion and by loss of hypoxic vasoconstriction. Accordingly, at this stage, the pulmonary artery pressure should be near normal.

Low lung weight: Only ground-glass densities are present on CT scan, primarily located subpleurally and along the lung fissures. Consequently, lung weight is only moderately increased.

Low lung recruitability: The amount of non-aerated tissue is very low; consequently, the recruitability is low.[5]

COVID-19 pneumonia- H Type

High elastance: The decrease in gas volume due to increased edema accounts for the increased lung elastance.

High right-to-left shunt: This is due to the fraction of cardiac output perfusing the non-aerated tissue which develops in the dependent lung regions due to the increased edema and superimposed pressure.

High lung weight: Quantitative analysis of the CT scan shows a remarkable increase in in lung weight (> 1.5 kg), on the order of magnitude of severe ARDS.[6]

High lung recruitability: The increased amount of non-aerated tissue is associated, as in severe ARDS, with increased recruitability.[5]

Clinical Features of COVID-19 ARDS: In respiratory distress from COVID, patients initially retain relatively good compliance despite very poor oxygenation.[7,8] Minute ventilation is characteristically high. Infiltrates are often limited in extent and, initially characterized by a ground-glass pattern on CT that signifies interstitial rather than alveolar edema. Many patients do not appear dyspneic. These patients can be assigned, in a simplified model, to "type L," characterized by low lung elastance (high compliance), lower lung weight as estimated by CT scan, and low response to PEEP.[9] For many patients, the disease may stabilize at this stage without deterioration while others, either because of disease severity and host response or suboptimal management, may transition to a clinical picture more characteristic of typical ARDS. These can be defined as "type H," with extensive CT consolidations, high elastance (low compliance), higher lung weight, and high PEEP response. Clearly, types L and H are the conceptual extremes of a spectrum that includes intermediate stages, in which their characteristics may overlap. Another feature consistently reported is a highly activated coagulation cascade, with widespread micro- and macro-thromboses in the lung and in other organs; very elevated serum D-dimer levels are a consistent finding associated with adverse outcomes.[10] These observations indicate the fundamental roles played by disproportionate endothelial damage that disrupts pulmonary vasoregulation, promotes ventilation-perfusion mismatch (the primary cause of initial hypoxemia), and fosters thrombogenesis. In addition, remarkably increased respiratory drive and energy loads from a patient's respiratory effort applied to highly vulnerable tissue, adding P-SILI to the mix of the lung's inflammatory assault.[11,12] When confronting such an unfamiliar and rapidly evolving environment, only certain aspects of well-accepted lung-protective approaches to ARDS remain rational at these different stages. More important, in attention to the vascular side (eg, avoidance of fluid overload, reduction of cardiac output demands) could inadvertently promote counterproductive responses (eg, edema) and iatrogenic damage.

Ventilator Management in COVID-19 ARDS: In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options for providing enhanced respiratory support include HFNC, NIPPV, intubation and invasive mechanical ventilation, or ECMO.

Ventilator management offered to Type L and Type H patients are different (Table-2).

1. The first step to reverse hypoxemia is through an increase in FiO_2 to which the Type L patient responds well
2. In Type L patients with dyspnea, several noninvasive options are available: HFNC), CPAP) or NIV. At this stage, the measurement (or the estimation) of the inspiratory esophageal pressure swings is crucial.[13] In the absence of the esophageal manometry, surrogate measures of work of breathing, such as the swings of central venous pressure[14] or clinical detection of excessive inspiratory effort, should be assessed. In intubated patients, the P0.1 and $P_{occlusion}$ should also be determined. High PEEP, in some patients, may decrease the pleural pressure swings and stop the vicious cycle that exacerbates lung injury. However, high PEEP in patients with normal compliance may have detrimental effects on hemodynamics. In any case, noninvasive options are questionable, as they may be associated with high failure rates and delayed intubation, in a disease which typically lasts several weeks.
3. The magnitude of inspiratory pleural pressures swings may determine the transition from the Type L to the Type H phenotype. As esophageal pressure swings increase from 5 to 10 cmH_2O which are generally well tolerated to above 15 cmH_2O, the risk of lung injury increases and therefore intubation should be performed as soon as possible.
4. Once intubated and deeply sedated, the Type L patients, if hypercapnic, can be ventilated with volumes greater than 6 ml/kg (up to 8 ml/kg), as the high compliance results in tolerable strain without the risk of VILI. Prone positioning should be used only as

Table 1. L & H Phenotypes

Variations of COVID-19			
	L-Phenotype		H-Phenotype
Low Elastance (High Compliance)	Nearly normal compliance - nearly normal amount of gas in the lungs	High Elastance (Low Compliance)	Increased edema – Decreases gas volumes & Increases lung elastance
Low Ventilation Perfusion ratio	Low V/Q Ratio – Hypoxemia may be due to perfusion regulation loss & Hypoxic Vasoconstriction	High Right to left Shunt	Due to fraction of Cardiac output perfusing non-aerated dependent lung regions
Low Lung Weight	Subpleural ground glass opacities on CT only moderately increase lung weight	High Lung Weight	Remarkable increases in lung weight on CT is comparable to severe ARDS
Low Recruitability	Amount of non-aerated tissues is very low - recruitability is low	High Recruitability	Increased amount of non-aerated tissue is associated with increased recruitability

a rescue maneuver, as the lung conditions are "too good" for the prone position effectiveness, which is based on improved stress and strain redistribution. The PEEP should be reduced to 8–10 cmH_2O, given that the recruitability is low and the risk of hemodynamic failure increases at higher levels. An early intubation may avert the transition to Type H phenotype.

5. Type H patients should be treated as severe ARDS, including higher PEEP with identifying optimal PEEP, if compatible with hemodynamics, prone positioning and extracorporeal support.

The Phenotype Type L (Image-1) and Type H (Image-2) patients are best identified by CT scan and are affected by different pathophysiological mechanisms. If not available, signs which are implicit in Type L and Type H definition could be used as surrogates: respiratory system elastance and recruitability. Understanding the correct pathophysiology is crucial to establishing the basis for appropriate treatment.

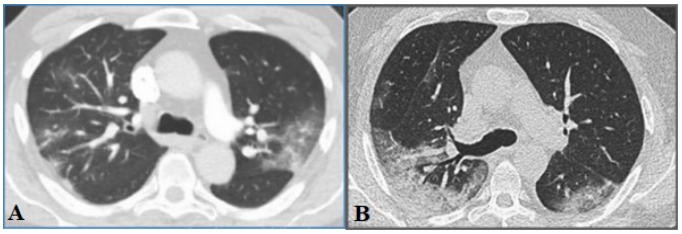


Image 1. L-Phenotype: A: Demonstrate multifocal peribronchial ground-glass opacity, B: Demonstrate multifocal ground-glass opacity and consolidation

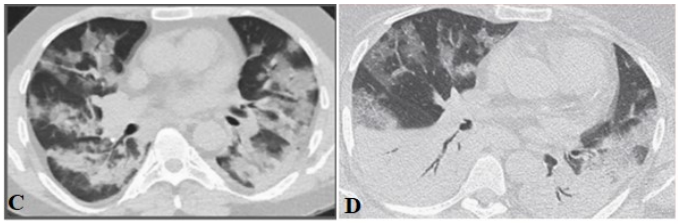


Image-2: H-Phenotype: C: Demonstrate mixed ground-glass opacity and consolidation, D: Geographic distribution of mixed Confluent consolidations and interlobular septal thickening

Mode of ventilation: The mode of ventilation was reported in 5/26 studies. In four of them the choice was volume-controlled ventilation [15, 17, 19, 22] while in the fifth study pressure-controlled ventilation was used in 52% and volume-controlled ventilation in 19% of the cases [16].

Tidal volume: TV was reported in 13/26 studies. The values of TV per predicted body weight varied from 5.6 to 7.5 ml/Kg.[23,25]

Respiratory rate: RR was reported in 10/26 studies and ranged from 20 to 33 breaths/min.[15,16 ,20]

PEEP: All but three of the studies reported PEEP with median values that ranged from a minimum of 9 cmH_2O to a maximum of 16.5 cmH_2O[20]; only two of the studies reported a median value lower than 10 cmH_2O.

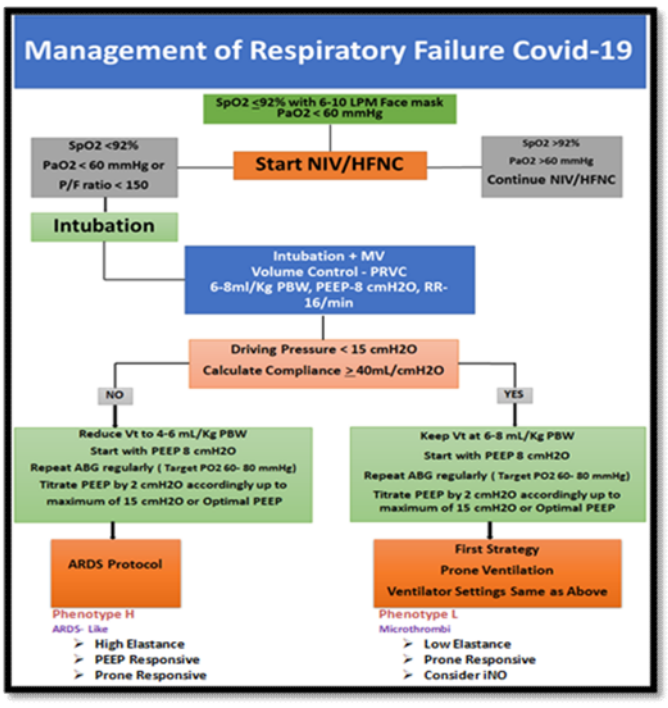
Plateau pressure: Plateau pressures, which were reported in 18/26 studies ranged from 20.5 to 31 cmH_2O.[18,21]

Driving pressure: Driving pressures were reported in 17/26 studies and ranged from 9.5 to 15 cmH_2O.[20, 24]

Static compliance*:* Static respiratory system compliance was reported in 20/26 studies. The values reported showed wide variability, ranging from 24[18] to 49 ml/cmH_2O[21,24], although the range was slightly more narrow, from 27 to 41 ml/cmH_2O, in studies that included more than 100 patients .[15]

Recommendations for management of COVID-19-associated ARDS: 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 differ ently to PEEP levels and fluid management.[28,29] Identifying recruitability with a simple bedside technique could help to tailor ventilatory management in patients with ARDS, including those with COVID-19.[26,30] 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.[27] 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[31] 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.[32] 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.[33] Patients with the robust inflammatory response common in COVID-19 are probably biologically primed to develop ventilation-induced lung injury.[34] The respiratory system mechanics and risk of lung strain in these patients might worsen quickly, especially with the resumption of spontaneous efforts to breathe.[35] 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.

Table 2. Ventilator Management



Protecting the COVID-19-associated ARDS Lung: Patients with type L CARDS, having good lung compliance, accept larger tidal volumes (6-8 mL/kg ideal body weight) than those customarily prescribed for ARDS without worsening the risk of VILI.

Plateau pressure of less than 30 cm H2O and driving pressure of less than 15cm H2O, both are accepted thresholds for VILI protection. Higher VT could help avoid reabsorption atelectasis and hypercapnia due to hypoventilation with lower tidal volumes. The key issue in this early stage is disrupted vasoregulation, where the pulmonary vasoconstriction that normally occurs in response to hypoxia fails to occur because of an endothelial assault that mismatches perfusion to ventilation and may result in profound hypoxemia. If respiratory drive is not reduced by oxygen administration and noninvasive support, persistently strong spontaneous inspiratory efforts simultaneously increase tissue stresses and raise pulmonary transvascular pressures, vascular flows, and fluid leakage (ie, P-SILI).[36-38] Early intubation, effective sedation, and/or paralysis may interrupt this cycle. Targeting lower PEEP (8-10 cm H2O) is appropriate. Raising mean transpulmonary pressures by higher PEEP or inspiratory-expiratory ratio inversion redirects blood flow away from overstretched open airspaces, accentuating stresses on highly permeable microvessels and compromising CO2 exchange without the benefit of widespread recruitment of functional lung units. If lung edema increases in the type L patient, either because of the disease itself and/or P-SILI, the baby lung shrinks further, and the type H phenotype progressively develops. Concentrating the entire ventilation workload on overtaxed baby lung increases its power exposure and blood flow, there by accentuating its potential for progressive injury. There are 2 major contributors to this VILI vortex of shrinking the baby lung: airspace VILI[36] and intensified stresses within the vessels that perfuse it.[37,38] Over a period of time, superimposed VILI and unchecked viral disease incite inflammation and edema, promoting local and generalized thrombogenesis, intense cytokine release, right ventricular overload, and systemic organ dysfunction. In this advanced state, it is advisable to apply a more conventional lung-protective strategy: higher PEEP (15 cm H2O), lower tidal volume (4-6 mL/kg), and prone positioning while minimizing oxygen consumption.

Prone position ventilation and Recruitment: Using prone positioning in severe COVID-19 patients to prevent the deterioration of patients' condition (Grade 1+, strong recommendation). Rationale prone positioning has a beneficial effect on oxygenation, lung recruitment, and stress distribution. The physiological effects of prone positioning include redistribution of lung densities, often with the recruitment of well-perfused dorsal regions. Although prone positioning increases chest wall elastance, this change is usually accompanied by improved lung recruitment, a reduction in alveolar shunt and improved ventilation/perfusion ratio, subsequent improvement in oxygenation and CO2 clearance, a more homogeneous distribution of ventilation and a reduced VILI risk.[39, 40] Indications for prone positioning include moderate to-severe ARDS (PaO2/FiO2 < 150 mmHg), and/or hypercapnia. Duration of prone positioning should be more than 16 hours, and the termination of prone positioning should be based on the response of oxygenation, lung mechanics, and hemodynamics. Because prone positioning could improve lung in homogeneity, early prone positioning should be provided for COVID-19 infected patients with/without respiratory failure[41,42] since it could prevent respiratory failure. Since COVID-19 is highly infectious, implementation of the prone positioning might require more manpower, thus further increasing the workload of medical personnel. Pressure injury of the skin and mucous, facial edema, corneal edema, displacement of the catheter, and airway obstruction must be avoided when placing patients in the prone position. Since we know prone position itself is a recruitment to open up the non-aerated alveoli in a homogenous manner to improve oxygenation and also recruiting the lungs with sustained inflation pressure to iincrease the number of alveoli in the dependent part of the lungs participating in gas exchange, increase lung compliance and reduced intrapulmonary shunt improving gas exchange in pulmonary capillaries.[43] A sustained inflation is the recruitment maneuver that has been used most commonly. A common approach has been to set the ventilator to CPAP mode and increase the pressure to 35–40 cm H_2O for 35–40 s while monitoring the patient for signs of adverse effects, such as hemodynamic compromise.[44]

Evidence:Acute respiratory failure was the main indication for ICU admission, with 80% of our COVID-19 patients requiring invasive mechanical ventilation which is consistent with the experience in Lombardy, Italy[45], where 88% of ICU patients were intubated. While early single-center reports in small groups of COVID patients reported well-preserved lung mechanics despite the severity of hypoxemia[46], more recent data[47] and our observations suggested that lung compliance and driving pressure were close to those of reported in classical ARDS. As published in EClinical Medicine, Mittermaier et al and colleagues[48] investigated the effects of invasive mechanical ventilation, PEEP and prone positioning (PP) on oxygenation and lung recruitability in patients with COVID-19-related ARDS. All three interventions led to markedly improved oxygenation in COVID-19-related ARDS. Initiation of invasive mechanical ventilation also led to a significant reduction in opacity indices assessed by chest X-ray indicating lung recruitability. Despite low numbers in the groups, it becomes clear that PEEP and PP are able to improve oxygenation in COVID-19-related ARDS. As for classical ARDS, we think that there are more doubts than certainties on the correct setting of PEEP 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 and in COVID19-ARDS[49], and there is growing evidence of increased alveolar dead space[50] and limited recruitability in COVID-19-ARDS[51]. Second, there is a worryingly high incidence of barotrauma and gas leak manifestations (pneumothorax and pneumomediastinum) in COVID-19-ARDS patients[52,53], which is probably because of specific characteristics of the lung parenchyma (so-called 'lung frailty').[54]

In a case series of 16 mechanically ventilated patients with COVID-19, Gattinoni et al and colleagues[55] 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 PEEP strategy. Gattinoni et al and colleagues[56] recommended the use of tidal volumes greater than 6 mL/kg predicted body weight 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. They 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. Therefore, 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 6–8 mL/kg) predicted body weight, as the high compliance results in tolerable strain without the risk of ventilator-induced lung injury.

CONCLUSIONS

The available literature shows patients with acute respiratory failure related to COVID-19, ventilation with a lower VT and prone positioning is applied more rigorously than in patients with ARDS from another origin. COVID-19 causes unique lung injury. It may be helpful to categorize patients as having either type L or H phenotype. Different ventilatory approaches are needed, depending on underlying pathophysiology. Applied positive end–expiratory pressures and oxygen fractions were higher in patients with acute respiratory failure related to COVID-19. It is likely that lung protection is of equal importance in COVID-19 patients as it is in patients with ARDS from another origin. With few exceptions, COVID-19-ARDS patients should be ventilated with usual lung protective settings, constituting low tidal volumes (4-6 ml/kg PBW), plateau pressures lower than 30 cmH2O, airway driving pressures lower than 15 cmH2O as in classical ARDS.

Abbreviations

ARDS: Acute respiratory distress syndrome
CARDS: COVID-19-related ARDS
VILI: Ventilator induced lung injury
VT: Tidal volume
PEEP: Positive end-expiratory pressure
P-SILI: Pulmonary transvascular pressures, vascular flows, and fluid leakage
HFNC: High-flow nasal cannula
CPAP: Continuous positive airway pressure
NIV: Noninvasive ventilation
ECMO: Extracorporeal membrane oxygenation.

REFERENCES

1. The Italian Thoracic Society (AIPO - ITS) and Italian Respiratory Society (SIP/IRS). Managing the Respiratory Care of Patients with COVID-19. Version - March 08, 2020:
2. Phua J, Weng L, Ling L et al(2020)Intensive care management of corona virus disease2019 (COVID19):
3. Alhazzani W, Møller MH, Arabi YM et al (2020) Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). Intensive Care Med.
4. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M (1987) Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. The American review of respiratory disease. .
5. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G (2006) Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med.*
6. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G (2006) Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med.*
7. Grasselli G, Zangrillo A, Zanella A, et al; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020. Published online April 6, 2020.
8. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020. Published online March 19, 2020.
9. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med*. 2020.
10. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020.
11. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med.* 2017.
12. Marini JJ, Rocco PRM, Gattinoni L. Static and dynamic contributors to ventilator-induced lung injury in clinical practice. pressure, energy, and power. Am J Respir Crit Care Med. 2020.
13. Gattinoni L, Giosa L, Bonifazi M, Pasticci I, Busana M, Macri M, Romitti F, Vassalli F, Quintel M (2019) Targeting transpulmonary pressure to prevent ventilator-induced lung injury.
14. Walling PT, Savege TM (1976) A comparison of oesophageal and central venous pressures in the measurement of transpulmonary pressure change. *Br J Anaesth.*
15. Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020.
16. Botta M, Tsonas AM, Pillay J, et al. Ventilation management and clinical outcomes in invasively ventilated patients with COVID-19 (PRoVENT-COVID): a national, multicentre, observational cohort study. *Lancet Respir Med.* 2020.
17. Schenck EJ, Hoffman K, Goyal P, Choi J, Torres L, Rajwani K, Tam CW, Ivascu N, Martinez FJ, Berlin DA. Respiratory mechanics and gas exchange in COVID-19-associated respiratory failure. *Ann Am Thorac Soc*. 2020.
18. Sinha P, Calfee CS, Cherian S, et al. Prevalence of phenotypes of acute respiratory distress syndrome in critically ill patients with COVID-19: a prospective observational study. *Lancet Respir Med.* 2020.
19. Beloncle FM, Pavlovsky B, Desprez C, Fage N, Olivier P-Y, Asfar P, Richard J-C, Mercat A. Recruitability and effect of PEEP in SARS-Cov-2-associated acute respiratory distress syndrome. Ann Intensive Care. 2020.
20. Diehl J-L, Peron N, Chocron R, et al. Respiratory mechanics and gas exchanges in the early course of COVID-19 ARDS: a hypothesis-generating study. *Ann Intensive Care.* 2020.
21. Bos LDJ, Paulus F, Vlaar APJ, Beenen LFM, Schultz MJ. Subphenotyping acute respiratory distress syndrome in patients with COVID-19: consequences for ventilator management. Ann Am Thorac Soc. 2020.
22. Zangrillo A, Beretta L, Scandroglio AM, et al. Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan, Italy. *Crit Care Resusc.* 2020.
23. Pedersen HP, Hildebrandt T, Poulsen A, Uslu B, Knudsen HH, Roed J, Poulsen TD, Nielsen HB. Initial experiences from patients with COVID-19 on ventilatory support in Denmark. *Dan Med J.* 2020.
24. Carsetti A, Damia Paciarini A, Marini B, Pantanetti S, Adrario E, Donati A. Prolonged prone position ventilation for SARS-CoV-2 patients is feasible and effective. Crit Care. 2020.
25. Liu X, Liu X, Xu Y, Xu Z, Huang Y, Chen S, Li S, Liu D, Lin Z, Li Y. Ventilatory ratio in hypercapnic mechanically ventilated patients with COVID-19-associated acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020.
26. Pan C, Chen L, Lu C, et al. Lung recruitability in SARS-CoV-2 associated acute respiratory distress syndrome: a single-center, observational study. *Am J Respir Crit Care Med* 2020.
27. Bos LD, Paulus F, Vlaar APJ, Beenen LFM, Schultz MJ. Subphenotyping ARDS in COVID-19 patients: consequences for ventilator management. Ann Am Thorac Soc 2020; published online May 12. DOI:10.1513/AnnalsATS.202004-376RL. ndrome: a single-center, observational study. *Am J Respir Crit Care Med* 2020.
28. Famous KR, Delucchi K, Ware LB, et al. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med* 2017.
29. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014.
30. Chen L, Del Sorbo L, Grieco DL, et al. Potential for lung recruitment estimated by the recruitment-to-inflation ratio in acute respiratory distress syndrome. A clinical trial. *Am J Respir Crit Care Med* 2020.
31. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000.
32. Hager DN, Krishnan JA, Hayden DL, Brower RG, for the ARDS Clinical Trials Network. Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005.
33. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA 2012.
34. Hoegl S, Burns N, Angulo M, et al. Capturing the multifactorial nature of ARDS—'two-hit' approach to model murine acute lung injury. Physiol Rep 2018:

35. Yoshida T, Fujino Y, Amato MBP, Kavanagh BP. Fifty years of research in ARDS. spontaneous breathing during mechanical ventilation. Risks, Mechanisms, and Management. *Am J Respir Crit Care Med* 2017.
36. Marini JJ, Rocco PRM, Gattinoni L. Static and dynamic contributors to ventilator-induced lung injury in clinical practice. pressure, energy, and power. *Am J Respir Crit Care Med.* 2020.
37. Vieillard-Baron A, Matthay M, Teboul JL, et al. Experts' opinion on management of hemodynamics in ARDS patients: focus on the effects of mechanical ventilation. *Intensive Care Med.* 2016.
38. Marini JJ, Hotchkiss JR, Broccard AF. Bench-to-bedside review: microvascular and airspace linkage in ventilator-induced lung injury. CritCare. 2003.
39. Santini A, Protti A, Langer T, Comini B, Monti M, Sparacino CC, et al. Prone position ameliorates lung elastance and increases functional residual capacity independently from lung recruitment. *Intensive Care Med Exp.* 2015..
40. Guerin C, Mancebo J. Prone positioning and neuromuscular blocking agents are part of standard care in severe ARDS patients: yes. *Intensive Care Med*. 2015.
41. Zochios V, Parhar K, Vieillard-Baron A. Protecting the right ventricle in ARDS: the role of prone ventilation. *J Cardiothorac Vasc Anesth.* 2018.
42. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med.* 2016.
43. Goligher EC, Hodgson CL, Adhikari NK, Meade MO, Wunsch H, Uleryk E, et al. 43. Lung recruitment maneuvers for adult patients with acute respiratory distress syndrome. A systematic review and meta-analysis. *Annals of the American Thoracic Society.*
44. Brower RG, Morris A, MacIntyre N, Matthay MA, Hayden D, Thompson T, et al. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Crit Care Med* 2003.
45. Grasselli G, Zangrillo A, Zanella A et al (2020) Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA.
46. Gattinoni L, Chiumello D, Caironi P et al (2020) COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 46:1099–1102.
47. Grasselli G, Tonetti T, Protti A et al (2020) Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study.
48. Mittermaier M, Pickerodt P, Kurth F, et al. Evaluation of PEEP and prone positioning in early COVID-19 ARDS. *E Clinical Medicine* 2020.
49. Grasselli G, Tonetti T, Protti A, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. *Lancet Respir Med* 2020.
50. Chiumello D, Busana M, Coppola S, et al. Physiological and quantitative CTscan characterization of COVID-19 and typical ARDS: a matched cohort study. *Intensive Care Med* 2020.
51. Ball L, Robba C, Maiello L, et al., GECOVID (GEnoa COVID-19) group. Computed tomography assessment of PEEP-induced alveolar recruitment in patients with severe COVID-19 pneumonia. Crit Care 2021.
52. Belletti A, Palumbo D, Zangrillo A, et al., COVID-BioB Study Group. Predictors of pneumothorax/pneumomediastinum in mechanically ventilated COVID-19 patients. *J Cardiothorac Vasc Anesth* 2021.
53. Belletti A, Landoni G, Zangrillo A. Pneumothorax and barotrauma in invasively ventilated patients with COVID-19. *Respir Med* 2021.
54. Lemmers DHL, Abu Hilal M, Bna C, et al. Pneumomediastinum and subcutaneous emphysema in COVID-19: barotrauma or lung frailty? *ERJ Open Res* 2020.
55. Gattinoni L, Coppola S, Cressoni M, Busana M, Chiumello D. Covid-19 does not lead to a 'typical' acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020.
56. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020.

****