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Mechanical ventilation in SARS-CoV-2 patients: state of art

Ventilación mecánica en pacientes con SARS - CoV-2: estado del arte

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Abstract

COVID-19-associated infection leads to a pathology of yet unknown clinical behavior, confronting the clinician with various challenges. An extensive search was conducted based on review articles on SARS-CoV-2 infection and studies including mechanical ventilation management strategies in order to complete this narrative review. Evidenced-based treatment for SARS-CoV2 infection is still in the works. We have some tools from our knowledge from past experiences indicating that a step-wise management approach should be used, without neglecting other joint therapeutic measures for improved clinical outcomes of a condition with a high mortality. The current recommendations indicate that patients with severe acute respiratory failure due to SARS-CoV-2 should be managed with protective mechanical ventilation measures. No strong evidence is yet available on the individualization of mechanical ventilation therapy according to phenotypes.

Keywords

SARS-CoV-2; Coronavirus; Acute respiratory distress syndrome; Critical care; Mechanical ventilation; SARS.

Resumen

La infección asociada a COVID-19 produce una patología de comportamiento aún desconocido, planteándole diversos desafíos al clínico. Para esta revisión narrativa se llevó a cabo una extensa búsqueda basada en artículos de revisión sobre la infección por SARS-CoV-2 y estudios que incluían estrategias de manejo con ventilación mecánica. El tratamiento basado en evidencia para la infección por SARS-CoV2 todavía está en desarrollo. Tenemos algunas herramientas basadas en nuestros conocimientos de experiencias en el pasado que indican que se debe usar un abordaje escalonado, sin descuidar otras medidas terapéuticas conjuntas para mejorar los desenlaces clínicos de una condición con una elevada mortalidad. Las actuales recomendaciones indican que los pacientes con falla respiratoria aguda por SARS-CoV-2 deben manejarse con medidas de protección con ventilación mecánica. Aún no tenemos una sólida evidencia sobre la individualización del tratamiento con ventilación mecánica, de acuerdo a los distintos fenotipos.

Palabras clave

SARS-CoV-2; Coronavirus; Síndrome de dificultad respiratoria aguda; Cuidado crítico; Ventilación mecánica; SARS.

INTRODUCTION

SARS-CoV-2 infection is responsible for the current pandemic, which has claimed many lives worldwide (1) given its high level of contagiousness (2). Approximately 14% develop a serious disease that requires hospitalization and oxygen support (3); the most frequent diagnosis in severe patients is severe pneumonia with progression to Acute Respiratory Distress Syndrome (ARDS) in up to 30% of cases (4), which has required management with mechanical ventilation in intensive care units (ICU) (5).

Severe SARS-CoV-2 disease was initially described in China (6) where 1099 patients were identified, of whom a small percentage developed acute respiratory distress syndrome (ARDS), septic shock, and multiple organ failure. These patients were treated with invasive / non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO). The cohort study (7) evidenced a high burden of the disease and patients required ICU management because of their age (> 60 years), the presence of comorbidities such as hypertension (31.2% of the cases), cardiovascular disease (14.5%), diabetes (10.1%), inter alia. The SOFA SCORE indicated significant acute physiological dysfunction, with compromised pulmonary function with moderate to severe PAO_2/FIO_2 , according to the ARDS Berlin classification. However, the behavior of ARDS in SARS-CoV-2 patients is baffling (Image 1), and differs from the established definition. (8) The behavior is atypical by day 8 after the onset of the infection, and up to 50% of the cases exhibit normal pulmonary compliance, which has raised reasonable doubt as to whether we are dealing with atypical ARDS, which increasingly presents in younger patients (9-13).

From the histopathological perspective, ARDS is a heterogeneous condition. (14,15) Diffuse alveolar damage during the organization phase has been described in the case of SARS-CoV-2 infection (16), in addition to micro and macro thrombosis phenomena associated with the respiratory

process produced by the virus, leading to the pathophysiology of hypoxemia. This may also be related to the description of the phenotypes, multisystemic phenomena and proinflammatory processes probably associated with multi-organ dysfunction syndrome and fatal outcomes. (17) Dr. Gattinoni describes 2 different phenotypes that may present dynamically in the same patient: a low phenotype, accounting for 70-80% of the cases, characterized by a low V / Q ratio, few opacities in the chest images, low lung weight, and low elastance / high compliance. The other less frequent high phenotype is exactly the opposite, characterized by right-to-left shunt, four-quadrant opacities on chest images – the so called “white lung” -, high elastance / low compliance, and high lung weight. Although the clinical behavior and the pathophysiological phenomena responsible for each phenotype are different, both may present with severe hypoxemia, hence requiring a different therapeutic approach. (18,19)

WHAT MECHANICAL VENTILATION STRATEGIES ARE AVAILABLE FOR SARS-COV-2 PATIENTS?

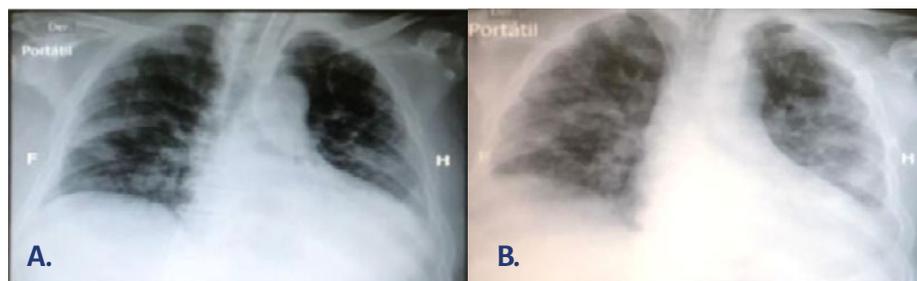
The SARS-CoV-2 infection is a new pathology, so the evidence is just being developed and there is not yet a correct therapeutic approach. The principles of mechanical ventilation are to improve gas

exchange, decrease the patient's respiratory work, and buy time while re-establishing respiratory and systemic physiology. The decision to ventilate a patient will depend on multiple factors clinicians have to weigh at a certain point in time, such as ICU beds availability, the patient's prognostic factors, and his/her current clinical condition (20) (GRADE - Low level of evidence; conditioned recommendation). Patients with SARS-CoV-2 infection, and critically ill patients in general, experience a dynamic condition that may change abruptly; therefore, any interventions and decisions are constantly changing.

Non-invasive mechanical ventilation (NIV) and high flow nasal cannula (HFNC)

During a pandemic, additional strategies to invasive mechanical ventilation are described. (21) Non-invasive mechanical ventilation is not recommended in the management guidelines for patients with COVID-19, who are hypoxemic and in respiratory failure, because of the high risk of transmission and particle dispersion (22,23); however, a document based on the experience of the COVID-19 outbreak in China highlights the use of non-invasive mechanical ventilation in patients with ARDS and $PAO_2/FIO_2 > 150$ mmHg. (24) This approach should be restricted to units where only suspected or confirmed patients with COVID-19 are hospitalized,

IMAGE 1. Patients with acute hypoxemic respiratory failure confirmatory of SARS-CoV2- infection. **A.** L Phenotype. **B.** H Phenotype.



SOURCE: Authors.

provided there is adequate ventilation or negative pressure, no interface leakage (a full-face mask is mandatory) and the staff in the area should use proper aerosol protection measures. When this is not possible, mechanical ventilation with orotracheal intubation should be preferred. (25)

Some studies report the use of high flow cannula (60L/min) for patients with severe pneumonia, wearing a surgical mask over the interface to avoid aerosolization; some articles discuss the low risk of aerosolization and suggest its use in selected cases. (26)

Several literature reports indicate the use awake pronation in patients with mild to moderate ARDS, and the results have been encouraging in terms of improved oxygenation parameters and lower intubation rates (27); however, the evidence to date is not conclusive to support these strategies for widespread management. What is clear is that patients who do not require intubation, should not be intubated early (28), nor should intubation be delayed in those patients with the potential to develop complications. (29)

In some circumstances, HFNC and non-invasive NIV may fail, so early intubation should be considered: (24)

1. PaO₂ / FiO₂ ≤150 mmHg,
2. Hypoxemia that does not improve after 1 hour of NIV.
3. Vigorous spontaneous efforts (tidal volume > 12 ml / Kg of ideal weight), due to the risk of P-SILI.
4. ROX index <4,88 at 12 h (for high flow nasal cannula)

Invasive mechanical ventilation

The indications for orotracheal intubation are the same as in patients with respiratory failure from other causes (30); in particular, in the SARS-CoV2 patient the decision will depend to a large extent on his/her clinical symptoms. There have been cases of silent hypoxemia (31), rapid hypoxemia and refractory to management with high flow oxygen, without any additional

manifestations. It is important to mention that one of the most relevant indications to initiate mechanical ventilation is increased respiratory work, since vigorous respiratory effort in a patient with an established lung injury may lead to the development of P-SILI (Patient-Self-Inflicted Lung Injury). (32)

Consider tracheal intubation if the patient has:

1. Increased respiratory work
2. Tachypnea > 30 rpm persistent
3. Refractory hypoxemia: O₂ saturation <90% despite supplemental oxygen (FiO₂ ≥50%)
4. Acute respiratory failure
5. Shock criteria
6. An altered state of consciousness

If intubation is considered an option, it should be performed as soon as possible, otherwise the patient may experience a rapid decline. (24,33)

Mechanical ventilation is not a therapy per se; it is considered a therapeutic strategy aimed at gaining time until the symptoms resolve, and it is part of the management armamentarium that includes conservative and individualized fluid strategy, the use of neuromuscular blockers, sedation, nutrition, glycemic control, steroid use, ECMO, and experimental drug therapies. (29) The use of an individualized mechanical ventilation strategy is recommended. (34,35) Dr. Gattinoni's study, recommends starting with an individualized mechanical ventilation strategy, according to the phenotype. The low phenotype may call for a tidal volume (TV) strategy of 8-9 mL / Kg of ideal weight, PEEP 8-10 cmH₂O, use the prone rescue maneuver, use of hemodynamic and ventilatory monitoring, not forgetting those patients with low recruitment and oxygen saturation goals ranging between 92-96%. In contrast, the high phenotype could benefit from a TV 6 mL / Kg, PEEP > 10cmH₂O, prone positioning is mandatory; these are patients with a high probability of recruitment and their lung involvement results in lower oxygen saturation, ranging

from 88-92%. (18) These are simply some recommendations from the experts in the above-mentioned study, but the evidence is not strong enough. A study published in Lancet in 2019 concluded that the personalized mechanical ventilation strategy according to the type of ARDS, focal or diffuse, made no difference in mortality. Personalizing mechanical ventilation did not decrease mortality in ARDS, possibly due to the misclassification of 21% of the patients in this study. Therefore, further studies are needed in this area. (36) The management of ARDS in the patient with SARS-CoV-2 infection is extrapolated from the ARDS management guidelines for other causes (37,38).

WHICH THERAPEUTIC STRATEGIES HAVE THE STRONGEST EVIDENCE IN COVID-19 ARDS PATIENTS ("CARDS")?

The knowledge of the ventilatory strategies for SARS-COV2 infection is mainly extrapolated from the accumulated evidence in ARDS.

Evidence-based treatment of SARS-COV2 infection is still in the works.

Protective mechanical ventilation

Protective mechanical ventilation is defined as ventilation in which the tidal volume is low, that is, 6 mL / Kg of ideal weight, to maintain a plateau pressure (P_{plat}) <28 cmH₂O and a driving pressure (DP) <15 cmH₂O (39), (GRADE; Strong recommendation; moderate level of evidence 1B), which impacts mortality in this clinical setting. (40) The starting point should be 100% FIO₂ and decrease every 20-30 minutes from 5 to 5%, monitoring the patient's clinical condition, avoiding hyperoxia due to the toxic and deleterious effect. (41,42) Tidal volume should be calculated based on ideal weight; the

formula for men: $50 + 0.91$ (size -152.4); and for women: $45.5 + 0.91$ (size -152.4) (43)

The goal of protective ventilation is not to correct the blood gas disorder but to lower the risk of ventilator-induced lung injury (VILI). Patients usually do not tolerate such low volumes, so in general, the use of sedation and neuromuscular blockers are necessary to avoid ventilator asynchrony, which can further impair lung damage.(44) ventilator

The recommendation is to set the respiratory rate to 20-25 breaths / min, the inspiratory time in the volume-controlled mode should be 0.7 - 0.8 seconds to avoid decreasing the inspiratory flow since they are inversely proportional ($\text{Flow} = \text{Volume} / \text{time}$); however, in the pressure-controlled mode it should be around 1 second to ensure that the alveolar pressure at the end of inspiration reaches the programmed pressure and a tidal volume of 6 ml / Kg is delivered, allowing adequate alveolar filling and emptying, taking into account the time constants, to avoid auto-PEEP(45)

Pressure-controlled versus volume-controlled ventilation

No differences have been reported between volume-controlled versus pressure-controlled mechanical ventilation. (46,47) In the setting of SARS-CoV-2 infection, mechanical ventilation monitoring is recommended to assess the best mode and ventilation strategy. (48, 49) Given the need for mechanical ventilation monitoring, the volume-controlled mode with square or constant flow wave is preferable.

No differences were found between pressure-controlled and volume-controlled modes in terms of compliance, gas exchange, hemodynamic variables, respiratory work, mortality, or ICU stay in ventilated patients with acute respiratory distress syndrome(46).

The lack of large randomized trials in SARS-CoV-2 limits our knowledge to decide which ventilation mode should be used and the evidence is still evolving. Initially, patients with severe hypoxemia and

average compliance caught our attention, and suggested different phenotypes. Later, as the disease progressed, its similarity to a typical acute respiratory distress syndrome was identified, with different mechanical characteristics explained by the natural course of the disease. The recommendation is to adhere to the scientific evidence showing good results in ARDS patients, providing protective ventilation and positive pressure at the end of individualized expiration regardless of the ventilation mode selected. (50)

Considering that the literature does not report superiority of one ventilatory mode over the other, the decision should be made on the basis of different considerations, such as the patient's condition over the natural course of the disease and the specific characteristics of the respiratory system (which are dynamic); the experience of the healthcare staff with a particular mode of ventilation, allowing for appropriate patient-ventilator synchrony, until the lung recovers, with the least possible damage associated with invasive mechanical ventilation programming.

Prone position

Pronation is not recommended for every ARDS patient. The guidelines recommend the use of prone positioning for at least 12 hours per day in moderate/severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$ mmHg GRADE; Strong recommendation; moderate-high level of evidence 1A-B) (51)

The PROSEVA study showed a reduction in mortality with pronation for 16 consecutive hours for 4 days, in moderate/severe ARDS.(52) Several meta-analyses support the pronation in this clinical setting, particularly for more than 12 hours and in association with protective mechanical ventilation strategies. (53,54)

The substantial benefit should be considered in the context of the significant risk of occurrence of adverse events (endotracheal tube displacement, pressure ulcers, and loss of venous access), although

the evidence was low or very low to support these findings.(51)

Prone therapy begins with a specific protocol, ideally from 12 to 16 hours and its continuity will depend on the patient's response. There is no standard time for the duration of pronation since the studies have different periods of duration ranging from 4 to 7 days. Others suggest discontinuation based on the response to the number of sessions, which are usually variable. (55,56) According to the literature a favorable response to prone positioning in the first few hours is a predictor for success, but initial non-response does not rule out success. (56)

Prone positioning is discontinued in case of a favorable response defined as a $\text{PAO}_2/\text{FIO}_2 > 150$ mmHg for at least 4 hours, in the supine position after the last prone session with $\text{PEEP} < 10$ cmH₂O and $\text{FIO}_2 < 60\%$. (52) In the PROSEVA study, stopping prone therapy should be considered when the patient presents a deterioration in oxygenation (decrease in $\text{PAO}_2/\text{FIO}_2 > 20\%$ for the supine position if accidental extubation occurs, sustained decrease in oxygenation for 5 minutes ($\text{SatO}_2 < 85\%$ or $\text{PaO}_2 < 55$ mmHg with $\text{FIO}_2 100\%$), hemodynamic instability or cardiorespiratory arrest.(56) In the case of cardiorespiratory arrest in the prone position, there are no specific recommendations on cardiopulmonary-cerebral resuscitation, although some case reports indicate that it is possible to start in the prone position for the first cycles and then proceed to position the patient in the supine position to continue resuscitation(57).

The lack of large randomized trials in SARS-CoV-2 limits our knowledge about prone positioning. Some retrospective studies confirm the benefits of pronation in this subgroup of patients, but more evidence is required. (58-59)

High peep versus low peep.

The lack of large randomized trials in SARS-CoV-2 restrict the knowledge of the PEEP. The evidence is of low quality to

support the use of higher PEEP strategies in moderate or severe ARDS (conditioned). There are inconsistencies due to the differences in the results of the studies in terms of the heterogeneity of the strategy to establish the level of PEEP, while some trials compared lower tidal volume ventilation as part of a ventilator strategy that included lower levels high PEEP. The recommendation to consider higher PEEP in moderate ARDS is based on data from individual and subgroups of patients. The risk of barotrauma may not be ruled out because it has not been quantified in this population(51). A recent study concluded that for ARDS patients who responded to increased PEEP with better oxygenation, hospital and ICU 28-day mortality could be reduced, without increasing the risk of clinically documented barotrauma. (60) The recommendation is to estimate the optimal PEEP to achieve the best compliance. (51) A new expert opinion document indicated that for patients with SARS-CoV-2, PEEP levels should be limited to 8-10 cmH₂O, since higher levels will not increase pulmonary compliance and negatively impact the venous return, causing more harm than benefit. Bedside echocardiography may prove to be useful in assessing right heart function while managing PEEP increases.(61)

According to the Colombian ARDS consensus, the initial approach for PEEP should be guided by the PEEP / FIO₂ table (GRADE; Strong recommendation; moderate level of evidence 1B). (62,63) Other titration methods for PEEP include the volume pressure curve, the best compliance, the stress index (=1), transpulmonary pressure, or image-guided (CT, ultrasound) best driving pressure. (61) The consensus suggests the use of driving pressure for PEEP titration (GRADE; Moderate level of evidence; weak recommendation 2B). PEEP should be neither too high (produces overdistension and increased dead space) nor too low (produces de-recruitment and atelectrauma). PEEP titration should avoid increases in plateau pressure, thus ensuring a decrease in driving pressure(24).

If available, the use of volumetric capnography for PEEP titration is suggested in moderate to severe ARDS (GRADE; Low level of evidence; very weak recommendation 2C) (63) There is no conclusive evidence on volumetric capnography in COVID-19.

Recruitment maneuvers

There is limited knowledge about recruitment maneuvers due to the lack of large randomized trials in SARS-CoV-2. Alveolar recruitment maneuvers (ARM) should not be used in ARDS routinely (GRADE; Strong of Recommendation Against). (37) In cases of de-recruitment (due to endotracheal aspiration, disconnection) or refractory hypoxemia, despite optimizing therapy, alveolar recruitment maneuvers could be performed. (64) There are multiple alveolar recruitment maneuvers, however, the evidence indicates that there is no one maneuver that is superior to another. (65) Not all patients with ARDS are potentially recruitable or respond to recruitment, and this variability is due to various factors(66), such as the cause of ARDS (higher in secondary ARDS or of extrapulmonary origin) (67), the evolutionary phase (early) (68), the position of the patient (higher in pronation, because of increased transpulmonary pressure in the dorsal region and improved gas exchange) (67), vasoactive management (69) (changes in cardiac output and pulmonary blood flow distribution theoretically affect the response to the maneuver), thoracic expansion capacity (ineffective in patients with reduced thoracic expansion capacity), and previously programmed ventilator parameters (70,71) (low tidal volume, high PEEP; since ARM are likely to start from a recruited lung). The studies fail to establish specific criteria to define a positive ARM response. According to Grasso (68) maneuver responders are patients in which the PAO₂/FIO₂ increases at least 50% after the maneuvers, while Villagr70 and Girgis(72) define responders as patient with

20% increase in PAO₂/FIO₂. Borges(73) reports a positive response when PaO₂ / FIO₂ > 350, with a collapsed lung tissue mass of less than 5%. The studies define the response in terms of lung mechanics, analyzing the effect of the maneuver on parameters such as lung compliance. (66)

The evidence in terms of improvement in clinical outcomes of ARM is controversial. A recent meta-analysis concluded that ARM could improve oxygenation but doesn't seem to improve survival(65).

Lung recruitment in SARS-CoV-2 can be assessed at the bedside, even in very constrained environments. An observational study claims that lung recruitability was low in 12 patients with COVID-19 ARDS, and alternating body positioning improved recruitability. A new mechanics-based index to directly quantify the potential for lung recruitment is the recruitment-to-inflation ratio (R/I ratio) ranging from 0 to 2.0; the higher the R/I ratio, the higher the potential for lung recruitment. An R/I ratio of 1.0 suggests a high likelihood of recruitment. These findings do not imply that all patients with SARS-CoV-2-associated ARDS are poorly recruitable, and both the severity and management of these patients can differ remarkably according to the region.(74)

Clinicians in Wuhan decided to systematically use this recruitment measure in a series of patients with SARS-CoV-2-associated ARDS, and to assess the effect of body positioning. (74) Further randomized studies with larger samples are needed to define the best recruitment maneuver and the specific indications in this group of patients.

Neuromuscular blockers

The ACURASYS study(75) showed improved mortality in ARDS with a PaO₂ / FIO₂ < 150 mmHg with the early use of a 48-hour infusion of cisatracurium and deep sedation versus deep sedation alone. The exact mechanism whereby neuromuscular blockade is beneficial is unclear. The lack

of large, randomized trials in SARS-CoV-2 is a limitation to our understanding of neuromuscular blockers.

The ROSE study(76) found that there was no significant difference in 90-day mortality between patients who received an early and continuous infusion of cisatracurium. The guidelines do not suggest the use of neuromuscular blockers for all patients with ARDS (GRADE: weakly recommendation against). The use of a 48-hour continuous infusion of cisatracurium besylate is suggested in early moderate/severe ARDS (PAO₂/FIO₂ <150 mmHg GRADE: weakly recommendation in favor)(37). Neuromuscular blockers can decrease barotrauma and hospital stay. (77,78) A 2018 review(79) found no difference between the different neuromuscular blocking agents vecuronium versus cisatracurium. Its use is particularly notable in patients with patient-ventilator asynchrony and PAO₂/FIO₂ <120mmHg(80)

A multicenter observational study of 407 patients with COVID-19 moderate to severe ARDS, found that NMBA were frequently used beyond the recommended period of time; however, after adjusting for confounders, there was no difference in the proportion of extubation rate according to NMBA length. (81)

WHAT RESCUE STRATEGIES HAVE BEEN STUDIED?

Patients with ARDS under a strategy of protective mechanical ventilation may present hypercapnia, which has been identified as having an impact on the clinical outcomes of patients, increasing mortality. (82-85) The knowledge of the ventilatory strategies for SARS-COV2 infection is extrapolated from the accumulated evidence in ARDS. Management is individualized, the strategies may include increasing the volume or respiratory rate according to tolerance, and extracorporeal CO₂ removal devices (ECCO₂R) in the patient's clinical context(86).

ECMO

Veno-venous extracorporeal membrane oxygenation is a rescue therapy in severe ARDS with potentially reversible hypoxemia, but refractory to conventional therapies. (37,87,88). The lack of large, randomized trials in SARS-CoV-2 limits the knowledge of ECMO.

The CESAR STUDY (89) concluded that ECMO therapy in experienced centers could improve survival without increased disability. A new EOLIA TRIAL(90) was published in 2018, and their conclusion was that mortality was not significantly lower with ECMO than with a conventional mechanical ventilation strategy. A meta-analysis (87) comparing conventional mechanical ventilation versus venous-venous ECMO concluded that ECMO was associated with reduced 60-day mortality. However, venous-venous ECMO was also associated with a moderate risk of major bleeding. Particularly, in the SARS-CoV-2 infection scenario, the evidence is scarce, but the experience in previous pandemics has provided preliminary guidance for the use of ECMO and the recommendation is to indicate its use in selected patients with refractory hypoxemia and potential PAO₂/FIO₂ <80mmHg recovery, with no contraindications and in places with extensive ECMO experience.

Data from 213 hospitals worldwide, with 1035 patients with COVID-19 who received ECMO support, provide a generalizable estimate of ECMO mortality in the setting of COVID-19. The Extracorporeal Life Support Organization (ELSO) Registry concluded that in patients with COVID-19 who received ECMO, both estimated mortality 90 days after ECMO and mortality in those with a final disposition of death or discharge were less than 40%. (91)

More studies are required to determine the risk-benefit of ECMO therapy in patients with severe SARS-Cov-2 infection.(92)

Extracorporeal CO₂ removal

Extracorporeal CO₂ removal devices (ECCO₂R) allow CO₂ to be extracted from venous blood by passing it through a membrane similar to that used in ECMO, but which uses much lower blood flow rates, and the arterial and venous cannulas are therefore smaller.(93) The lack of large randomized trials in SARS-CoV-2 limits the knowledge of ECCO₂T.

The Xtravent study (94) compared protective mechanical ventilation versus ultraprotective mechanical ventilation + ECCO₂R. In a post hoc analysis of the subgroup of patients with PaO₂ / FiO₂ <150 mmHg, treatment with ultra-protective mechanical ventilation + ECCO₂R was found to significantly reduce the number of days without mechanical ventilation. A systematic review (95) found no overall differences in mortality, days of ICU stay, or days without mechanical ventilation. According to the literature, the role of ECCO₂R in clinical practice could be in the subgroup of patients with ARDS with PaO₂ / FiO₂ > 80mmHg and <150 mmHg, in which conventional support treatment and ventilation has been optimized to the maximum without response, and in those who are required to minimize pulmonary bloating and / or mitigate the effects of hypercapnia and acidosis.(93) In the SARS-Cov-2 infection scenario, there is insufficient evidence available. There is currently a study in the recruitment phase, to investigate the efficacy of extracorporeal CO₂ elimination for the correction of hypercapnia in ARDS associated with COVID-19 disease (SARS-CoV-2). The results from this study will provide new knowledge in this regard.(96)

A case report highlights the use of ECCO₂R in severe ARDS and refractory hypercapnia associated with COVID19. Future studies are required to further investigate its safety and efficacy. (97,98)

What is the evidence-based management and the most appropriate clinical approach?

The management of SARS-CoV-2 associated ARDS requires the expertise of the clinician and quick decision-making, with an individualized approach to ensure the best outcomes. (99) Different ventilatory approaches are needed, depending on the underlying physiology of the SARS-CoV2 infection.(100)

Table1 summarizes the available evidence for the management of ARDS and SARS-Cov2 infection. A schematic approach to managing the patient with SARS-CoV-2 acute respiratory failure is described in Figure 1.

CONCLUSIONS

SARS-CoV-2 infection gives rise to a pathology of yet unknown clinical behavior, challenging the clinician in the context of the pandemic. ARDS exhibits heterogeneous clinical and histopathological characteristics and defy intensivists when implementing therapeutic strategies. Mechanical ventilation is part of the spectrum of therapeutic measures to "buy time" while the pathophysiological processes are normalized. A better understanding of the phenotypes and the underlying physiology is needed to help define ventilator parameters.

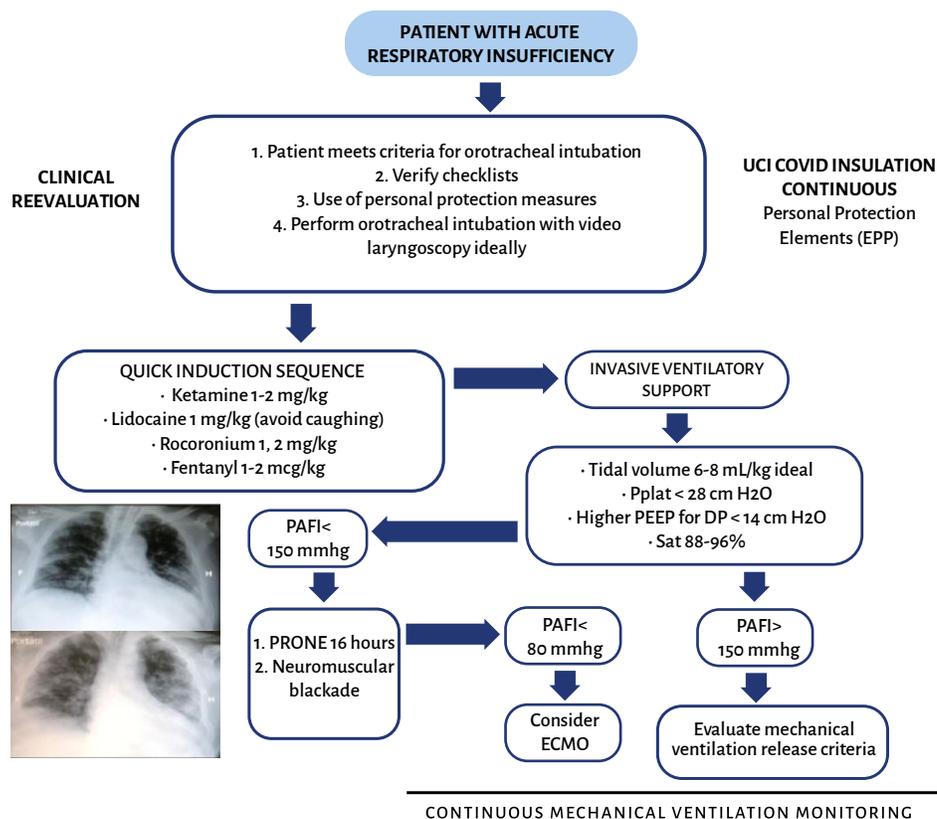
Evidence-based treatment of SARS-CoV-2 infection is still in the works; however, our knowledge from past experience favors a step-wise management approach, without neglecting other joint therapeutic measures to improve the clinical results of a condition with a high risk of mortality.

The current recommendations indicate that patients with severe acute respiratory failure due to SARS-CoV-2 should be managed with protective mechanical ventilation measures. No strong evidence is yet available on the individualization of mechanical ventilation therapy according to phenotypes.

TABLE 1. Summary of evidence-based interventions.

Intervention	ARDS severity	Grade evidence quality	Recommendation level	References
Lung protective ventilation	All patients with ARDS COVID-19*	Moderate	Strong	Aoyama et al 2019 (39) *Marini et al 2020 (100)
Prone position	ARDS Severe COVID-19*	Moderate-high	Strong	Guerin et al 2013 (52) Fan et al 2017 (54) *Elharrar et al 2020 (58) *Weiss et al 2020 (59)
High peep	Moderate-severe ARDS	Moderate	Conditioned	Guo et al 2018 (60) Ortiz et al 2020 (63)
Recruitment maneuvers	Moderate-severe ARDS COVID-19*	Low-Moderate	Conditioned	Furyk et al 2017 (64) Kang et al 2019 (65) *Pan C 2020 (74)
Neuromuscular blockers	Severe ARDS COVID-19*	Moderate	Weak	Papazian 2010 (75) PETAL STUDY 2019 (76) Hua Y et al 2020 (77) Zheng et al 2020 (78) *Courcelle et al 2020 (81)
Non-invasive mechanical ventilation and high flow cannula	Patients with mild respiratory failure in COVID19	Low	Conditioned	Patel et al 2020 (21)
ECMO	Severe ARDS COVID-19*	Does not apply	Does not apply	Munshi et al 2019 (87) *Barbaro et al 2020 (91) *Cho et al 2020 (92)

SOURCE: Adapted from Fan et al(54).

FIGURE 1. Therapeutic approach to the patient with acute respiratory failure for SARS-CoV-2.

SOURCE: Adapted from Shang Y, et al (24); Phua J, et al (29); Cook TM, et al (30); Wiersinga J, et al (86).

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Author Contributions

DAR: Study concept and design, Acquisition, analysis and interpretation of data, Drafting of the manuscript, Critical revision of the manuscript for important intellectual content, Original material and construction of images and tables, Administrative, technical, and material support, Study supervision.

BDGP: Acquisition, analysis and interpretation of data, Drafting of the manuscript, Study supervision.

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DREP: Study concept and design, Study supervision.

JCGM: Study concept and design, Critical revision of the manuscript for important intellectual content, Original material and construction of images and tables, Study supervision.

MAF: Acquisition, analysis and interpretation of data, Drafting of the manuscript, Administrative, technical, and material support, Study supervision, English translation.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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The authors have no potential conflict of interests to disclose.

REFERENCES

- Spina S, Marrazzo F, Migliari M, et al. The response of Milan's Emergency Medical System to the COVID-19 outbreak in Italy. *Lancet*. 2020;395:e49-50. doi: [http://dx.doi.org/10.1016/S0140-6736\(20\)30493-1](http://dx.doi.org/10.1016/S0140-6736(20)30493-1).
- Team NCPERE. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China. *China CDC Weekly*. 2020;2(8):113-22. doi: <https://doi.org/10.3760/cma.j.isn.0254-6450.2020.02.003>
- Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. 2020;102433. doi: <https://doi.org/10.1016/j.jaut.2020.102433>
- Wax R, Christian M. Practical Recommendations for Critical Care and Anesthesiology Teams Caring for Novel Coronavirus (2019-nCoV) Patients. *Can J Anaesth*. 2020;67(5):568-76. doi: <https://doi.org/10.1007/s12630-020-01591-x>
- Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2020. doi: <https://doi.org/10.1093/cid/ciaa270>
- Wei-jie Guan, Zheng-yi Ni, Yu Hu, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382:1708-20. doi: <https://doi.org/10.1056/NEJMoa2002032>
- Wang D, Hu B, Hu C, et al. Clinical Character-

- ristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323:1061-9. doi: <https://doi.org/10.1001/jama.2020.1585>.
8. Ranieri VM, Rubenfeld G, Thompson T, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-33. doi: <https://doi.org/10.1001/jama.2012.5669>
 9. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not?. *Critical Care* 2020;24:154. doi: <https://doi.org/10.1186/s13054-020-02880-z>
 10. Hassan K, Mandeep R Mehra. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. *J Heart Lung Transplant*. 2020;39(5):405–7. doi: <https://doi.org/10.1016/j.healun.2020.03.012>
 11. Copin MC, Parmentier E, Duburcq T, et al. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. *Intensive Care Med*. 2020;46(6):1124-6. doi: <https://doi.org/10.1007/s00134-020-06057-8>.
 12. Bellani G, Laffey J, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788-800. doi: <https://doi.org/10.1001/jama.2016.0291>
 13. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-43. doi: <https://doi.org/10.1001/jamainternmed.2020.0994>
 14. Katzenstein AL, Bloor C, Leibow A. Diffuse Alveolar Damage- The Role of Oxygen, Shock, and Related Factors. *Am J Pathol*. 1976;85(1):209–28.
 15. Lorente J, Cardinal P, Muñoz D, et al. Acute respiratory distress syndrome in patients with and without diffuse alveolar damage: an autopsy study. *Intensive Care Med*. 2015;41(11):1921-30. doi: <https://doi.org/10.1007/s00134-015-4046-0>. Epub 2015 Sep 18
 16. Zang H, Zhou P, Wei Y, et al. Histopathologic Changes and SARS-CoV-2 Immunostaining in the Lung of a Patient With COVID-19. *Annals of Internal Medicine*. 2020;172(9):629-632. doi: <https://doi.org/10.7326/M20-0533>
 17. Joly B, Siguret V, Veyradier. Understanding pathophysiology of hemostasis disorders in critically ill patients with COVID-19. *Intensive Care Med*. 2020;46:1603–6. doi: <https://doi.org/10.1007/s00134-020-06088-1>
 18. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes?. *Intensive Care Medicine*. 2020;46:1099–1102. doi: <https://doi.org/10.1007/s00134-020-06033-2>.
 19. Jain A, Doyle J. Stages or phenotypes? A critical look at COVID-19 pathophysiology. *Intensive Care Med*. 2020;46:1494–5. doi: <https://doi.org/10.1007/s00134-020-06083-6>
 20. Vincent JL, Taccone F. Understanding pathways to death in patients with COVID-19. *Lancet*. 2020;8(5):430-2. doi: [https://doi.org/10.1016/S2213-2600\(20\)30165-X](https://doi.org/10.1016/S2213-2600(20)30165-X)
 21. Patel B, Kress J, Hall J. Alternatives to Invasive Ventilation in the COVID-19 Pandemic. *JAMA*. 2020;324(1):43-44. doi: <https://doi.org/10.1001/jama.2020.9611>
 22. Consenso colombiano de atención, diagnóstico y manejo de la infección por SARS-COV-2/ COVID-19 en establecimientos de atención de la salud. Recomendaciones basadas en consenso de expertos e informadas en la evidencia. *Infectio*. 2020;24:3.
 23. Gómez C, Peñuelas O, Lujan M, et al. Documento de consenso. Recomendaciones de consenso respecto al soporte respiratorio no invasivo en el paciente adulto con insuficiencia respiratoria aguda secundaria a infección por SARS-CoV-2. *Medintensiva*. 2020;44(7):429-38. doi: <https://doi.org/10.1016/j.medin.2020.03.005>
 24. Shang Y, Pan Chun, Yang X. Management of critically ill patients with COVID-19 in ICU: statement from front-line intensive care experts in Wuhan, China. *Ann Intensive Care*. 2020;10:73. doi: <https://doi.org/10.1186/s13613-020-00689-1>
 25. Guía de la OPS para el cuidado crítico de pacientes adultos graves con coronavirus (COVID-19) en las Américas. 2020. [Citado 23 Agosto 2020]. Disponible en: https://www.paho.org/col/index.php?option=com_docman&view=download&alias=2295-guias-covid-19-cuidado-critico-abril-2020-abril-version-larga-v1&category_slug=covid-19&Itemid=688
 26. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. *Eur Respir J*. 2020;55:2000892. doi: <https://doi.org/10.1183/13993003.00892-2020>.
 27. Thompson A, Ranard B, Wei Y, et al. Prone Positioning in Awake, Nonintubated Patients With COVID-19 Hypoxemic Respiratory Failure. *JAMA Intern Med*. 2020;180(11):1537–9. doi: <https://doi.org/10.1001/jamainternmed.2020.3030>
 28. Tobin M, Laghi F, Jubran A. Caution about early intubation and mechanical ventilation in COVID-19. *Ann Intensive Care*. 2020;10:78 <https://doi.org/10.1186/s13613-020-00692-6>
 29. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. *Lancet*. 2020;8(5):506-17. doi: [https://doi.org/10.1016/S2213-2600\(20\)30161-2](https://doi.org/10.1016/S2213-2600(20)30161-2)
 30. Cook TM, Boghdady K, McGuire B, et al. Consensus guidelines for managing the airway in patients with COVID-19: Guidelines from the Difficult Airway Society, the Association of Anaesthetists the Intensive Care Society, the Faculty of Intensive Care Medicine and the Royal College of Anaesthetists. *Anaesthesia*. 2020;75(6):785-99. doi: <https://doi.org/10.1111/anae.15054>.
 31. Goldowitz I. Unusual characteristics of COVID-19: "happy hypoxemics". 2020. [Citado 23 agosto, 2020]. Disponible en: https://www.researchgate.net/post/Unusual_characteristics_of_COVID-19_happy_hypoxemics
 32. Yoshida T, Grieco D, Brochard L, et al. Patient self-inflicted lung injury and positive end-expiratory pressure for safe spontaneous breathing. *Curr Opin Crit Care*. 2020;26(1):59-65. doi: <https://doi.org/10.1097/MCC.0000000000000691>
 33. Manejo clínico del COVID-19: atención hospitalaria. Gobierno de España, Ministerio de Sanidad. 2020. Disponible https://www.msccbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Protocolo_manejo_clinico_ah_COVID-19.pdf
 34. Murthy S, Gomersall C, Fowler R, et al. Care for Critically Ill Patients With COVID-19. *JAMA*. 2020;323(15):1499-500. doi: <https://doi.org/10.1001/jama.2020.3633>
 35. Wunsch H. Mechanical Ventilation in

- COVID-19: Interpreting the Current Epidemiology. *Am J Respir Crit Care Med.* 2020;202(1):1–21. doi: <https://doi.org/10.1164/rccm.202004-1385ED>
36. Constatin JM, Jabaudon M, Lefrant JY, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. *Lancet.* 2019. doi: [https://doi.org/10.1016/S2213-2600\(19\)30138-9](https://doi.org/10.1016/S2213-2600(19)30138-9)
37. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. *Ann. Intensive Care.* 2019;9:69. doi: <https://doi.org/10.1186/s13613-019-0540-9>
38. Silvio A Ñamendys-Silva. Respiratory support for patients with COVID-19 infection. *Lancet.* 2020;8(4):E18. doi: [https://doi.org/10.1016/S2213-2600\(20\)30110-7](https://doi.org/10.1016/S2213-2600(20)30110-7)
39. Aoyama H, Uchida K, Aoyama K, et al. Assessment of Therapeutic Interventions and Lung Protective Ventilation in Patients With Moderate to Severe Acute Respiratory Distress Syndrome: A Systematic Review and Network Meta-analysis. *JAMA Netw Open.* 2019;2(7):e198116. doi: <https://doi.org/10.1001/jamanetworkopen.2019.8116>
40. Weiss CH, M.cSparron J, Chatterjee R, et al. Summary for clinicians: mechanical ventilation in adult patients with acute respiratory distress syndrome clinical practice guideline. *Ann Am Thorac Soc.* 2017;14(8):1235–8. doi: <https://doi.org/10.1513/AnnalsATS.201704-332CME>
41. Girardis M, B.usani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU randomized clinical trial. *JAMA.* 2016;18;316(15):1583–9. doi: <https://doi.org/10.1001/jama.2016.11993>
42. Walkey AJ, Del Sorbo L, Hodgson C, et al. Higher PEEP versus lower PEEP strategies for patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *Ann Am Thorac Soc.* 2017;14(Suppl 4):S297–303. doi: <https://doi.org/10.1513/AnnalsATS.201704-338OT>
43. Durante G, Turco M, Rustichini L, et al. ARDS-Net lower tidal volume ventilatory strategy may generate intrinsic positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Resp Crit Care Med.* 2002;165:1271–4. doi: <http://dx.doi.org/10.1164/rccm.2105050>
44. Carrasco R, Villamizar G, Fernández M. Ventilator-Induced Lung Injury (VILI) in Acute Respiratory Distress Syndrome (ARDS): Volutrauma and Molecular Effects. *Open Respir Med J.* 2015;9:112–9. doi: <https://doi.org/10.2174/1874306401509010112>
45. Bein T, Grasso S, Moerer O, et al. The standard of care of patients with ARDS: ventilatory settings and rescue therapies for refractory hypoxemia. *Intensive Care Med.* 2016;42:699–711. doi: <https://doi.org/10.1007/s00134-016-4325-4>
46. Rittayamai N, Katsios C, Beloncle F, et al. Pressure-Controlled vs Volume-Controlled Ventilation in Acute Respiratory Failure: A Physiology-Based Narrative and Systematic Review. *Chest.* 2015;148(2):340–55. doi: <https://doi.org/10.1378/chest.14-3169>
47. Chacko B, Peter J, Tharyan P, et al. Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). *Cochrane Systematic Review.* 2015. doi: <https://doi.org/10.1002/14651858.CD008807.pub2>
48. Chica-Meza C. Peña L, Villamarín H, et al. Cuidado respiratorio en COVID-19. *Acta Colomb Cuid Intensivo.* 2020;20(2):108–17. doi: <https://doi.org/10.1016/j.acci.2020.04.001>
49. Carter C. Osborn M, Agagah G, et al. COVID-19 Disease: invasive ventilation. *Clinics in Integrated Care.* 2020;1:100004. doi: <https://doi.org/10.1016/j.intcar.2020.100004>
50. Fan E, Beitler J, Brochard L, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *The Lancet Respiratory Medicine.* 2020;8(8):816–21. doi: [https://doi.org/10.1016/S2213-2600\(20\)30304-0](https://doi.org/10.1016/S2213-2600(20)30304-0)
51. Griffiths M. McAuley D, Perkins G, et al. Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Resp Res.* 2019;6:e000420. doi: <https://doi.org/10.1136/bmjresp-2019-000420>
52. Guerin C, Reignier J, Richard JC, et al. PRO-SEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med.* 2013;368:2159–68. doi: <https://doi.org/10.1056/NEJMoa1214103>
53. Park SY, Kim H, Yoo K, et al. The efficacy and safety of prone positioning in adults patients with acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. *J Thorac Dis.* 2015;7(3):356–67. doi: <https://doi.org/10.3978/j.issn.2072-1439.2014.12.49>
54. Fan, E, Del Sorbo L, Goligher E, et al. An Official American Thoracic Society/European Society of intensive Care Medicine/Society of Critical Care Medicine Clinical practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2017;195(9):1253–63. doi: <https://doi.org/10.1164/rccm.201703-0548ST>.
55. Gattinoni L, Taccone P, Carlesso E, et al. Prone Position in Acute Respiratory Distress Syndrome. Rationale, Indications, and Limits. *Am J Respir Crit Care Med.* 2013;188(11):1286–93. doi: <https://doi.org/10.1164/rccm.201308-1532CI>
56. Rodríguez R, Ordoñez S, Gómez J, et al. Prone position in the Acute Respiratory Distress Syndrome, physiology to clinical practice. *Medicas UIS* 2016;29(2). doi: <http://dx.doi.org/10.18273/revmed.v29n2-2016008>
57. Bhatnagar V, Jinjil K, Dwivedi D, et al. Cardiopulmonary Resuscitation: Unusual Techniques for Unusual Situations. *J Emerg Trauma Shock.* 2018;11(1):31–7. doi: https://doi.org/10.4103/JETS.JETS_58_17
58. Elharrar X, Trigui Y, Dols A, et al. Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. *JAMA.* 2020;323(22):2336–8. doi: <https://doi.org/10.1001/jama.2020.8255>
59. Weiss T, Cerda F, Scott B, et al. Positioning for patients intubated for severe acute respiratory distress syndrome (ARDS) secondary to COVID-19: a retrospective observational cohort study. *British Journal of Anaesthesia.* 2021;126(1):48–55. doi: <https://doi.org/10.1016/j.bja.2020.09.042>
60. Guo L, Xie J, Huang Y, et al. Higher PEEP improves outcomes in ARDS patients with clinically objective positive oxygenation response to PEEP: a systematic review and meta-analysis. *BMC Anesthesiology.* 2018;18:172. doi: <https://doi.org/10.1186/s12871-018-0631-4>
61. Gattinoni L. Preliminary observations on the ventilatory management of ICU COVID-19 patients. 2020. [Citado 23 agosto, 2020]. Disponible en: <https://www.pedsanesthesia.org/wp-content/uploads/2020/03/Ventila>

- [tor-Management Covid-19-ICU-EXPERT-OPI-NION-Gattinoni.pdf](#)
62. Taylor B, Bernard G. Lower Tidal Volume / Higher PEEP Reference Card for ARMA and ALVEOLI Studies. *Crit Care Clin.* 2011;27(3):459-68. doi: <https://doi.org/10.1016/j.ccc.2011.05.011>
 63. Ortiz G, Dueñas C, Garay M, et al. Consenso Colombiano de SDRA. *Acta Colomb Cuid Intensivo.* 2020; 20:200-52. doi: <https://doi.org/10.1016/j.acci.2020.03.001>
 64. Furyk, J. What are the effects of recruitment maneuvers for adults with acute respiratory distress syndrome receiving mechanical ventilation?. *Cochrane Clinical Answers.* 2017. doi: <https://doi.org/10.1002/cca.1606>
 65. Kang H, Yang H, Tong Z. Recruitment maneuvers for adults with acute respiratory distress syndrome receiving mechanical ventilation: a systematic review and meta-analysis. *J Crit Care.* 2019;50:1-10. doi: <https://doi.org/10.1016/j.jcrc.2018.10.033>.
 66. Algaba A, Nin N, GT-IRA of the SEMICYUC, et al. Alveolar recruitment maneuvers in respiratory distress syndrome. *Med Intensiva.* 2013;37(5):355-62. doi: <https://doi.org/10.1016/j.medine.2013.01.006>
 67. Pelosi P, Gama de Abreu M, Rocco PR. New and conventional strategies for lung recruitment in acute respiratory distress syndrome. *Crit Care.* 2010;14:210. doi: <https://doi.org/10.1186/cc8851>
 68. Grasso S, Mascia L, Del Turco M, et al. Effects of recruiting maneuvers in patients with acute respiratory distress syndrome ventilated with protective ventilatory strategy. *Anesthesiology.* 2002;96:795-802.
 69. Guerin C, Debord S, Leray V, et al. Efficacy and safety of recruitment maneuvers in acute respiratory distress syndrome. *Ann Intensive Care.* 2011;1:9. doi: <https://doi.org/10.1186/2110-5820-1-9>
 70. Villagr a A, Ochagav a A, Vatusa S, et al. Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2002;165:165-70. doi: <https://doi.org/10.1164/ajrccm.165.2.2104092>
 71. Kacmarek RM, Villar J. Lung recruitment maneuvers during acute respiratory distress syndrome: is it useful. *Minerva Anesthesiol.* 2011;77:85-9.
 72. Girgis K, Hamed H, Khater Y, et al. A decremental PEEP trial identifies the PEEP level that maintains oxygenation after lung recruitment. *Respir Care.* 2006;51:1132-9.
 73. Borges JB, Okamoto VN, Matos GF, et al. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006;174:268-78.
 74. Pan C. Lung Recruitability in COVID-19-associated Acute Respiratory Distress Syndrome: A Single-Center Observational Study. *Am J Respir Crit Care Med.* 2020;201(10):1294-7. doi: <https://doi.org/10.1164/rccm.202003-0527LE>
 75. Papazian L, Forel JM, Gacouin A, et al. ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med.* 2010;6:363(12):1107-16. doi: <https://doi.org/10.1056/NEJMoa1005372>
 76. Moss M, Huang D, Browe R, The National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. *N Engl J Med.* 2019;380:1997-2008. doi: <https://doi.org/10.1056/NEJMoa1901686>
 77. Hua, Y, Ou X, Li Q, et al. Neuromuscular blockers in the acute respiratory distress syndrome: A meta-analysis. *PlosONE.* 2020;15(1):e0227664. doi: <https://doi.org/10.1371/journal.pone.0227664>
 78. Zheng Z, Jiang L, Zhang S, et al. Neuromuscular blocking agents for acute respiratory distress syndrome: an updated meta-analysis of randomized controlled trials. *Respir Res.* 2020;21(1):23. doi: <https://doi.org/10.1186/s12931-020-1287-4>
 79. Torbic H, Krishnan S, Duggal A. Neuromuscular blocking agents for acute respiratory distress syndrome: how did we get conflicting results? *Crit Care.* 2019;23:305. doi: <https://doi.org/10.1186/s13054-019-2586-3>
 80. Matthay M, Aldrich J, Gotts J. Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet.* 2020;8(5):433-4. doi: [https://doi.org/10.1016/S2213-2600\(20\)30127-2](https://doi.org/10.1016/S2213-2600(20)30127-2)
 81. Courcelle R, Gaundry S, Serck N, et al. Neuromuscular blocking agents (NMBA) for COVID-19 acute respiratory distress syndrome: a multicenter observational study. *Crit Care.* 2020;24:446. doi: <https://doi.org/10.1186/s13054-020-03164-2>
 82. Nin N, Muriel A, Pe uelas O, et al. Severe hypercapnia and outcome of mechanically ventilated patients with moderate or severe acute respiratory distress syndrome. *Intensive Care Med.* 2017;43(2):200-8. doi: <https://doi.org/10.1007/s00134-016-4611-1>. Epub 2017 Jan 20
 83. Morales-Quinteros, Camprub  M, Bringu  J, et al. The role of hypercapnia in acute respiratory failure. *ICMx* 2019;7(Suppl 1):39. doi: <https://doi.org/10.1186/s40635-019-0239-0>
 84. Crystal GJ. Carbon Dioxide and the Heart: Physiology and Clinical Implications. *Anesth Analg.* 2015;121(3):610-23. doi: <https://doi.org/10.1213/ANE.0000000000000820>
 85. Tiruvoipati R, Pilcher D, Buscher H, et al. Effects of hypercapnia and hypercapnic acidosis on hospital mortality in mechanically ventilated patients. *Crit Care Med.* 2017;45(7):e649-56. doi: <https://doi.org/10.1097/ccm.0000000000002332>
 86. Wiersinga J, Rhodes A, Cheng A, et al. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA.* 2020;324(8):782-93. doi: <https://doi.org/10.1001/jama.2020.12839>
 87. Munshi L, Walkey A, Goligher E, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med.* 2019;7(2):163-72. doi: [https://doi.org/10.1016/S2213-2600\(18\)30452-1](https://doi.org/10.1016/S2213-2600(18)30452-1).
 88. Vincent JL. Annual Uptodate in Intensive Care and Emergency Medicine. *Extracorporeal Membrane Oxygenation.* Springer. 2020
 89. Peek G, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009;374(9698):1351-63. doi: [https://doi.org/10.1016/S0140-6736\(09\)61069-2](https://doi.org/10.1016/S0140-6736(09)61069-2)
 90. Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med.* 2018;378:1965-75. doi: <https://doi.org/10.1056/NEJMoa1800385>

91. Barbaro R, Madaren G, Boonstra P, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet*. 2020;396(10257):1071-8. doi: [https://doi.org/10.1016/S0140-6736\(20\)32008-0](https://doi.org/10.1016/S0140-6736(20)32008-0)
92. Cho H, Heinsar S, Jeong I, et al. ECMO use in COVID-19: lessons from past respiratory virus outbreaks—a narrative Review. *Critical Care*. 2020;24:301. doi: <https://doi.org/10.1186/s13054-020-02979-3>
93. Romay E, Ferrer R. Extracorporeal CO₂ removal: Technical and physiological fundamentals and principal indications. *Med Intensiva*. 2016;40(1):33-8. doi: <https://doi.org/10.1016/j.medine.2015.12.002>
94. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (approximately 3 ml/kg) combined with extracorporeal CO₂ removal versus 'conventional' protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. *Intensive Care Med*. 2013;39(5):847-56. doi: <https://doi.org/10.1007/s00134-012-2787-6>.
95. Fitzgerald M, Millar J, Blackwood B, et al. Extracorporeal carbon dioxide removal for patients with acute respiratory failure secondary to the acute respiratory distress syndrome: a systematic review. *Crit Care*. 2014;15;18(3):222. doi: <https://doi.org/10.1186/cc13875>
96. Low-flow Extracorporeal Carbon Dioxide Removal in COVID-19-associated Acute Respiratory Distress Syndrome. *ClinicalTrials.gov*. Identifier: NCT04351906
97. Boparai S, Steven K, Motayar N. Extracorporeal carbon dioxide removal in COVID-19 ARDS. *Chest*. 2020;158(4):A1029. doi: <http://dx.doi.org/10.1016/j.chest.2020.08.956>
98. Tully R, Hopley N, Lawrence G. The successful use of extracorporeal carbon dioxide removal as a rescue therapy in a patient with severe COVID-19 pneumonitis. *Anaesthesia Reports*. 2020;8:113-5. doi: <https://doi.org/10.1002/anr3.12072>
99. Accini J, Beltrán N, Nieto V, et al. Documento de consenso. Declaration of consensus in critical medicine for multidisciplinary care of the patient with a suspected or confirmed diagnosis of COVID-19. *Acta Colombiana de Cuidado Intensivo*. 2020;20(4):287-333. doi: <https://doi.org/10.1016/j.acci.2020.04.003>
100. Marini J, Gattinoni L. Management of COVID-19 Respiratory Distress. *JAMA*. 2020;323(22):2329-30. doi: <https://doi.org/10.1001/jama.2020.6825>