

A Quick Review on the Multisystem Effects of Prone Position in Acute Respiratory Distress Syndrome (ARDS) Including COVID-19

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ABSTRACT

OBJECTIVE: The purpose of this review is to highlight the multisystem effects of prone position in ARDS patients with a focus on current findings regarding its use in COVID-19 patients.

METHODS: Two reviewers comprehensively searched PubMed database for literature regarding pathophysiology and efficacy of prone position in ARDS patients as well as specific data regarding this approach in COVID-19 patients.

CONCLUSION: Prone positioning is well-documented to improve oxygenation and cardiac function in ARDS patients and might confer increased survival, with benefits that outweigh risks such as facial edema, endotracheal tube displacement, and intraabdominal organ dysfunction in obese patients. Severe COVID-19 pneumonia, while meeting ARDS criteria, differs from typical ARDS in several ways. Data would suggest that advantages of prone position would become limited after significant disease progression and fibrosis. The use of this technique in COVID-19 requires prolonged sessions that are unprecedented in the treatment of ARDS patients. New data regarding COVID-19 pathophysiology and patients continues to evolve daily. More frequently, patients are proned while maintaining spontaneous breathing—the results of this intervention are an area for future studies. There is more to learn about the appropriate use of prone position in COVID-19 patients. The multisystem risks and benefits require clinicians to adopt a patient centered decision-making algorithm when employing this technique in COVID-19 patients.

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Introduction

Acute respiratory distress syndrome (ARDS) is a clinical phenomenon characterized by severe hypoxemia with varied etiologies including sepsis and pneumonia.¹ Treatment of ARDS includes strategies that increase oxygenation while decreasing the risk of pulmonary barotrauma.² This includes lung protective therapies such as permissive hypercapnia and positive end expiratory pressure (PEEP).² Prone position is an adjunct therapy, that is, often employed in the treatment of ARDS.¹ It is a technique that dates back to the 1970s and has been demonstrated to improve V/Q mismatching in ARDS patients.^{1,3} The physiology includes a reduction in the difference in ventral dorsal transpulmonary pressures leading to homogeneous perfusion and recruitment of collapsed lung alveoli.³ In addition, prone position reduces dorsal lung compression, which usually occurs in the supine position.³ Several studies have demonstrated that early initiation of prone position (<48 hours after onset of ARDS) in addition to long proning sessions (>12 hours) provide significant improvement in oxygenation and might confer survival benefits for patients with severe ARDS (PaO₂/FiO₂ <100 mmHg).⁴⁻⁶

SARS-CoV-2 is a novel virus that causes severe acute respiratory distress syndrome and the disease known as COVID-19. The COVID-19 pneumonia is characterized by severe hypoxemia and often meets criteria for ARDS.⁷ Despite meeting this criteria however, COVID-19 pneumonia differs by relatively well-preserved compliance suggesting a possible loss of lung perfusion regulation ability.⁷ Treatment of this viral pneumonia has proven to be challenging for clinicians as so much of the disease process remains unknown. Prone position is a technique that has been utilized at some centers internationally as an adjunct treatment in COVID-19 patients who were mechanically ventilated or breathing spontaneously. While it is a readily employed clinical technique that can improve oxygenation, the use of prone position is not a benign intervention. With frequent repositioning, patients may be at an elevated risk for endotracheal tube or chest tube displacement, arrhythmias, and cardiac arrest. In addition, facial edema and pressure ulcers are common, especially with increased time spent in prone position. The purpose of this review is to highlight some of the multisystem effects of prone position in ARDS patients with a focus on current findings regarding the use of its use in COVID-19 patients.



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Methods

Two reviewers independently queried PubMed database for literature describing the pathophysiology and utilization of prone position in ARDS patients. Another search of the literature was conducted to explore the use of this technique in COVID-19 patients. Articles that met inclusion criteria were those which explored the multisystem effects of the prone position in ARDS or COVID-19 patients and discussed morbidity associated with proning. The COVID-19 literature was reviewed until April 2021.

Respiratory Effects

Respiratory effects in intubated patients

Sud et al⁵ demonstrated that prone position confers survival benefits in patients with severe ARDS receiving lung protective ventilation. More recent studies have demonstrated that prone position improves oxygenation in intubated COVID-19 patients.^{8,9} These studies observed a persistent increase in PaO₂/FiO₂ ratio after repeated prone position sessions.^{8,9} One of the primary mechanisms of improved oxygenation in prone position is the reduction in ventral-dorsal transpulmonary pressure difference.³ In the supine position, the dorsal lung tends to have greater pleural pressures than the ventral lung resulting in less expansion of the dorsal alveoli.^{3,10} As the dorsal lung receives the majority of the blood supply, this results in a ventilation/perfusion (V/Q) mismatch, that is, significantly exacerbated in ARDS due to even greater dorsal pleural pressures from pulmonary interstitial edema.^{3,10} In the prone position, the dorsal pleural pressures are reduced due to a combination of reduced lung compression by the heart and diaphragm as well as a gravitational redistribution of the excess interstitial fluids to ventral lung.^{3,10} A study in a subpopulation of morbidly obese patients showed improved oxygenation in the prone position when compared with nonobese patients.¹¹ This supports the notion that relieving the compressive effects of the heart and abdominal contents is a primary contributor to improving oxygenation in the prone position. Because blood supply is maintained to the dorsal lung, a more even V/Q ratio is achieved.^{3,10} Additionally, improved cardiac output, increased RV filling, and decreased pulmonary artery pressures lead to increased blood supply to the lungs allowing for improved gas exchange.^{10,12}

Based on the primary mechanisms mentioned above, the patients in which prone position seems to be most efficacious are those with diffuse pulmonary edema or dependent alveolar collapse.^{3,13} Although this may be the case in early COVID pneumonia, the later disease stages seem to manifest in significant pulmonary fibrosis noted by elevated IL-6 levels.^{14,15} This information would suggest that while prone position may benefit patients who present early in their disease course; the benefits may be limited once fibrosis has become more diffuse.

International centers have discovered that while coronavirus disease meets clinical criteria for ARDS under the Berlin definition,

patients display an atypical presentation of the syndrome.⁷ A study from an Italian center observed normal or high pulmonary compliance, which is usually indicative of lung parenchyma that can adequately oxygenate, in COVID-19 patients.⁷ The study suggests that this discrepancy in expected physiology could be due to severe hypoxemia in the setting of loss of compensatory pulmonary strategies such as hypoxic vasoconstriction.⁷ This manifests as hyperperfusion of alveoli that are not ventilated, producing a right to left intrapulmonary shunt.⁷ In ARDS patients, techniques to improve oxygenation including PEEP and prone position work by increasing alveoli recruitment.¹⁶ However, since compliance is maintained in COVID-19 patients, it is postulated that these techniques increase oxygenation through alteration of perfusion rather than ventilation to alleviate the intrapulmonary shunt.⁷

In another study, Gattinoni et al reconciled the discrepancy in COVID-19 presentation by categorizing the time-related pulmonary changes into 2 primary disease phenotypes. The first proposed phenotype is type L COVID-19 pneumonia, that is, seen during the early stages of disease.¹⁷ The type L phenotype is characterized by low elastance (high compliance), low ventilation-to-perfusion (VA/Q) ratio, low lung weight, and low lung recruitability.¹⁷ The type L phenotype can result in 2 possible outcomes: improvement of disease or progression to type H COVID-19 pneumonia.¹⁷ Type L progression to type H phenotype is due in part to patient self-inflicted lung injury (P-SILI).¹⁷ P-SILI is a phenomenon first described by Barach et al¹⁸ and Mascheroni et al¹⁹ and is characterized by interstitial lung edema secondary to negative inspiratory intrathoracic pressure and increased lung permeability. Interventions that could possibly prevent transition from type L to type H phenotype include increase in FiO₂, measurement or estimation of inspiratory esophageal pressure swings which can serve as a surrogate marker for increase risk of lung injury and need for intubation.¹⁷ Prone position is best used as a rescue intervention in the type L population, as these patients have low lung elastance (high compliance) and relatively well preserved lung parenchyma.¹⁷

The second disease phenotype known as type H is seen later in the disease course. Type H phenotype is characterized by high elastance (low compliance), high right to left shunt, high lung weight, and high lung recruitability.¹⁷ The pulmonary changes seen in COVID-19 pneumonia type H is potentially due to the evolution of the disease in addition to tissue injury secondary to prolonged high-stress ventilation.¹⁷ The type H phenotype meets criteria for severe ARDS under the Berlin definition, including hypoxemia, bilateral infiltrates on imaging, and decreased respiratory system compliance.^{17,20} Since type H patients meet criteria for severe ARDS, these patients benefit from interventions that are historically used in the treatment of severe ARDS.¹⁷ These include high PEEP, prone position, and extracorporeal support.¹⁷

The literature has demonstrated that not all COVID-19 patients have low lung recruitability, hence it is important to

identify which patients would benefit from maneuvers such as prone position. Pan et al²¹ described a quantitative bedside assessment that can be used to estimate potential for lung recruitment in mechanically ventilated patients. The index is known as the recruitment-to-inflation ratio (R/I ratio) and can be conducted using a single-breath maneuver on a ventilator.²¹ A higher R/I ratio correlates with high likelihood of lung recruitment.²¹ Pan et al demonstrated that using the R/I ratio, they were able to identify patients with poor lung recruitment (low R/I ratio). The study observed an increase in R/I ratio and lung recruitability with prone position sessions.²¹

Respiratory effects in non-intubated patients

Prone position is typically employed in intubated and sedated patients.^{1,3} At the start of the COVID-19 pandemic, prone position was used more frequently in non-intubated patients with varying results.²²⁻²⁵ Several studies demonstrated that prone position improves oxygenation in non-intubated patients.²²⁻²⁷ A single center study of 50 patients in a New York City Emergency Department demonstrated that self proning in non-mechanically ventilated patients, when used in tandem with supplemental oxygen, improved oxygenation.²³ The protocol at this center called for 30 to 120 minutes in the prone position.²³ Another study from a New York City center demonstrated improved oxygen saturation and P:F ratio in self proning, non-intubated patients.²⁴ Coppo et al²⁵ demonstrated that early initiation of prone position was associated with improvement in oxygenation, but the improvement in oxygenation was only maintained in 50% of patients after resupination. In a small single-center cohort study, Thompson et al²⁶ was able to demonstrate that the use of prone position in subset of patients was associated with lower intubation rates. The study found that patients whose oxygen saturation was sustained at 95% or higher after an hour of prone position had a 46% less chance of being intubated than their counterparts (patient's whose oxygen saturation remained at <95% after an hour of prone position).²⁶

The selection criteria for patients that would benefit from awake prone positioning vary among centers. Current literature recommends that prone position should not be utilized in non-intubated patients with severe respiratory failure ($\text{PaO}_2/\text{FiO}_2 < 100$) as this intervention could delay intubation in these patients.²² Furthermore, several studies recommend that patients who are hemodynamically unstable, have altered mental status and generally unable to follow directions are not candidates for awake prone positioning.²² Other contraindications to prone position in non-intubated patients are similar to those in intubated patients including facial trauma, spinal instabilities or fractures, pelvic fractures, and recent abdominal surgery resulting in increased intraabdominal pressure.^{22,28-30}

Another area that remains unclear due to limited data is the optimal duration of awake prone positioning. In the intubated

population, prolonged proning sessions (12-16 hours) are advocated.^{4,5,31,32} The duration of awake prone positioning is highly dependent on patient's comfort and ability tolerate the position; current findings suggest durations of 30 minutes to 8 hours.^{22,33} In a prospective, single-center study, Elharrar et al³⁴ showed that 63% of spontaneously breathing patients were able to tolerate prone position for more than 3 hours. While there is still more to learn regarding the use of awake prone positioning, current data suggest that the use of this intervention in conjunction with high flow nasal cannula or non-invasive ventilation (NIV) in the appropriate patient population can improve oxygenation and in some instances prevent intubation.^{22,25,26,30,33,35,36}

Cardiac Effects

Right ventricular dysfunction in the form of acute cor pulmonale (ACP) is a well-documented complication of ARDS.^{37,38} Some studies have documented that the prevalence of ACP is as high as 22% in ARDS patients.³⁸ The proposed pathophysiology of this phenomenon is 2-fold. The high airway pressures observed in ARDS can be transmitted to the alveoli resulting in high distending alveolar pressures.^{37,39} These increased pressures in the lung parenchyma are transmitted to the pulmonary arteries resulting in pulmonary hypertension.^{37,39} The second proposed mechanism is related to permissive hypercapnia, a protective ventilation strategy employed in ARDS patients. While permissive hypercapnia is protective against tidal hyper-ventilation, this strategy also results in pulmonary vasoconstriction and high pulmonary artery pressures.³⁷⁻⁴⁰ Mekontos Dessap et al³⁸ demonstrated that the prone position can mitigate these hemodynamic changes by decreasing airway pressures and reducing hypercapnia. In addition, several large studies have demonstrated that prolonged prone position improves cardiac index.^{12,41,42} This may be due to offloading of the right ventricle in the prone position and therefore an increase in venous return, specifically in preload dependent patients.^{10,42} Although arrhythmias have been observed during the immediate proning period, no studies were found demonstrating sustained arrhythmias or adverse effects associated with them.

COVID-19 pneumonia, although most recognized for its severe hypoxia and ARDS, has also been associated with a significant vasodilatory response and septic shock requiring vasopressors.^{43,44} An observational study from a New York City Center demonstrated that more than 50% of COVID-19 patients required vasopressors.⁴³ Systemic vasodilation secondary to the massive release of inflammatory cytokines by immune cells is a well-recognized aspect of the pathophysiology of septic shock. The subsequent hypoperfusion and tachycardia associated with vasopressors used to correct this state can lead to cardiac injury and ischemia. Additionally, numerous case reports have shown the hypercoagulable state and systemic inflammation now associated with the novel coronavirus has

led to thrombosis and myocardial infarctions.^{44,45} Studies have also demonstrated that SARS-CoV-2 is able to gain entrance into myocardial cells by binding to the angiotensin-converting enzyme 2 (ACE2) and cause direct toxicity that can result in acute cardiac injury.⁴⁶ The combination of direct and indirect cardiac injury caused by COVID-19 therefore may lead to both right ventricular dysfunction in the form of ACP as well as left ventricular dysfunction. Several studies have demonstrated that prone position improves cardiac index, mean arterial pressure, and specifically decreases right ventricular outflow impedance in ARDS patients.^{10,12,38,41,47} As the mechanism of cardiac dysfunction in ARDS and COVID-19 patients are similar, prone position might be an intervention that could alleviate the cardiac effects of SARS-CoV-2.⁴⁵

Intraabdominal Pressure, Renal, and Hepatic Function

Although prone position may cause an increase in intraabdominal pressures due to restricted movement of the abdomen, multiple studies have shown no significant decrease in renal function, perfusion, or hepatic clearing capacity.¹² These studies demonstrated that while the prone position in mechanically ventilated ARDS patients was associated with a small increase in renal vascular resistance, elevated pressures did not translate to clinically apparent pathology such as renal hypoperfusion.¹² As such, Hering et al¹² suggested that patients in the prone position do not require special support to decrease thoracic and abdominal compression. In another study, Hering et al⁴⁸ used hepatic clearance of indocyanine green dye (ICG) as a proxy for hepatic function in mechanically ventilated ARDS patients in the prone position. This study demonstrated that hepatic function was preserved in prone patients.⁴⁸ It should be noted these studies were performed in hemodynamically stable individuals without renal dysfunction and therefore may not be applicable to those with preexisting organ impairment. Another subset of patients that may not be able to tolerate this increase in intraabdominal pressures include those with abdominal obesity. Weig et al⁴⁹ found that patients with a sagittal abdominal diameter ≥ 26 cm have a higher risk of renal dysfunction and mortality when placed in prone position for a prolonged period of time.

Neurological Effects: Use of Neuromuscular Blockers

Many studies have demonstrated that prone position is most effective for the treatment of ARDS when sessions are lengthy (at least 12 hours)^{4,5,31,32} Early data from international centers report that the same holds true in prone position of COVID-19 patients.³² In order to successfully maintain mechanically ventilated patients in the prone position for these prolonged sessions, patients sometimes require infusions of neuromuscular blockers.³² Formerly, it was postulated that the use of neuromuscular blockers in conjunction with the use of corticosteroids in ARDS patients might result in ICU-acquired muscle weakness. Papazian et al⁵⁰ conversely illustrated that

early infusion of neuromuscular blockers, specifically initiation of cisatracurium within 48 hours of ARDS diagnosis improves survival and decreases morbidity without increasing muscle weakness.⁵⁰ In addition, this same clinical trial demonstrated that there was no difference in muscle strength between ARDS patients who received neuromuscular blockers in conjunction with corticosteroids as compared to patients who received neuromuscular blockers alone.⁵⁰ These findings from the literature suggest that the use of neuromuscular blocking agents in prone ARDS patients is safe and might provide survival benefits.^{50,51}

While data may be forgiving regarding the use of neuromuscular blocking agents, the same cannot be said for sedative agents that are needed in higher doses to avoid awareness while paralyzed and prone.²⁸ Multiple studies have shown increased depth of sedation leads to delayed time to extubation, chances of delirium, and risk of death.⁵²⁻⁵⁴

Morbidity and Adverse Effects

While the use of prone position is a seemingly benign clinical technique, many studies have illustrated adverse effects associated with proning.^{1,5} Abroung et al⁵⁵ suggested that the improvement in oxygenation provided by prone position might not translate to increased survival. This might be due to the fact that mortality in ARDS patient is usually secondary to multi-organ failure rather than refractory oxygenation.⁵⁵ In addition, the protective effects of the prone position might only confer temporary advantages.⁵⁵ Table 1 summarizes the multiorgan system effects of prone position.

Pressure ulcers, edema, tube displacement, and other complications

Pressure ulcers and facial edema were reported more frequently in the prone population.⁵⁶ Current data suggest that up to 57% of prone patients develop a pressure ulcer.⁵⁷ In a meta-analysis, Sud et al reiterated that prone position is more likely to be associated with pressure ulcers, obstruction of the endotracheal tube and dislodgement of the thoracostomy tube. Taccone et al⁵⁸ showed that patients in the prone position were more likely to experience complications including need for sedation, increased vasopressors, and device displacement as compared to supine patients. This same study demonstrated that the risk of complications statistically correlated to number of days in the prone position.⁵⁸ A New York City center highlighted some of the early complications identified in proned COVID-19 patients, including patient discomfort, pressure ulcers, and anxiety requiring sedation.²⁴ Other complications of prone position include ocular edema due to venous stasis and brachial plexus neuropathy.⁵⁹

A complication needing further exploration is the incidence of spontaneous pneumothorax and pneumomediastinum in COVID-19 patients. An increased incidence of these events was demonstrated with the previous SARS virus and continue anecdotally with the novel coronavirus.^{60,61} Whether this is due

Table 1. Effects of prone position on multiple organ systems.

Neurologic	No significant difference in muscle strength when paralytic agents used
	Increased need for sedation can lead to increased risk of death, delirium, delayed extubation
Cardiac	Improvement in venous return, cardiac index
	No significant risk of sustained arrhythmias while repositioning
Respiratory	Reduction in ventral-dorsal transpulmonary pressure difference
	Improvement in V/Q mismatch
Gastrointestinal	No clear increase in aspiration risk nor appropriate tolerance or tube feeding in prone position
Renal/hepatic	No significant decrease in renal or hepatic function or perfusion due to restricted movement of the abdomen in nonobese patients
	Potential for renal dysfunction in abdominal obesity
Other	Increased risk of pressure ulcers
	Increased incidence of endotracheal tube obstruction or dislodgement or chest tube

to the virus itself or due to pulmonary barotrauma from mechanical ventilation remains to be determined. Frequent repositioning in these patients therefore may theoretically predispose them to pneumothorax and its complications—although more studies are needed to evaluate the incidence relative to those in supine position.

Currently, there are no guidelines that provide recommendations for the appropriate duration and frequency of prone position sessions in COVID-19 or ARDS patients. A case report of 10 critically ill COVID-19 patients demonstrated that prolonged sessions (>16 hours and up to 36 hours) are safe and effective in increasing oxygenation in this patient population.⁶² Due to the prolonged proning sessions required for improved oxygenation in COVID-19 patients, these patients might be more susceptible to the aforementioned adverse effects.

Mortality

Table 2 summarizes the most commonly reported complications. While some earlier studies suggested no significant difference in mortality, patients from these studies were not placed in prone position for >10 hours per day.^{56,63} The PROSEVA study employed longer hours in the prone position and therefore found a reduction in mortality.

Enteral feeding and aspiration risk

There are limited studies that investigate the effects of enteral feeding in critically ill patients in the prone position. The current studies are equivocal, with some stating that there is no difference in gastric residual volume (GRV), a metric used to determine tolerance of enteral feeding, in supine and prone patients.^{64,65} Other studies note an increase in GRV in the prone position, noting that early initiation of enteral feeding in

prone patients results in a higher risk of aspiration events and vomiting.⁶⁶ Although there are no specific recommendations, current literature suggests center specific protocols which use established clinical techniques proven to decrease the risk of aspiration.⁶⁴ This includes elevation of the head of the bed, use of calorie dense feeding to decrease the volume of feeds, continuous feeding, and use of prokinetic agents such as erythromycin to aid gastric emptying.⁶⁴

Study Limitations

Limitations of this clinical review include the dynamic and unpredictable nature of COVID-19. The disease process and viral behavior is constantly evolving, with new information elucidated almost daily. This clinical review enlisted the limited literature, that is, currently present about this novel virus and pneumonia. While numerous data has been collected regarding prone position in ARDS, COVID-19 differs from typical ARDS and therefore more studies are needed still to determine the extent of the efficacy of prone positioning in this population.

Conclusion

The use of prone position is an adjunct therapy used in the treatment of ARDS that dates back to the 1970s. Several studies have demonstrated that proning ARDS patients improves oxygenation and might provide survival benefits. Specifically, the prone position improves cardiac index, decreases V/Q mismatching while preserving hepatic and renal function in nonobese patients. These data would suggest that the benefits of this approach in ARDS might outweigh the risks in this patient population. Early data from international centers report similar effects of prone position in COVID-19 patients. As it has well document adverse effects—facial edema, pressure ulcers, endotracheal tube dislodgement—it is up to clinicians to adopt patient centered

Table 2. Most commonly reported complications in major clinical studies.

STUDY, AUTHOR NAME	MOST COMMONLY REPORTED COMPLICATIONS
<i>"Effect of Prone Positioning on the Survival of Patients with Acute Respiratory Failure"</i> Gattinoni et al	Need for sedation
	Airway obstruction
	Facial edema
	Increased need for muscle relaxants
	Ventilator discoordination
	Transient desaturation
	Loss of venous access
	Accidental extubation
	**Only statistically significant complication compared to supine group was number of pressure sore per patient
<i>"Effects of Systematic Prone Positioning in Hypoxemic Acute Respiratory Failure"</i> Guerin et al	SpO ₂ < 85%
	Pressure sores
	SAP < 60 mmHg
	Cardiac arrest
	Heart rate < 30
	Hemoptysis
	Unplanned extubation
<i>"A Multicenter Trial of Prolonged Prone Ventilation in Severe Acute Respiratory Distress Syndrome"</i> Mancebo et al	Relatively low rate compared with the 2 studies mentioned above
	No statistically significant complications
<i>"Prone Positioning in Patients with Moderate and Severe Acute Respiratory Distress Syndrome"</i> Taccone et al	Need for increased sedation/muscle relaxants
	Vomiting
	Hypotension, arrhythmias, increased vasopressor requirements
	Loss of venous access
	Airway obstruction
	**All of the above were statistically significant and increased the more days spent in prone position
<i>"Prone Positioning in Severe Acute Respiratory Distress Syndrome"</i> Guerin et al	SpO ₂ < 85%
	SAP < 60 mmHg for >5 min
	Unscheduled extubation
	Heart rate < 30 for >1 min
	**No statistically significant complications, only cardiac arrest was statistically significant and greater in supine group

decision-making algorithm and weight the benefits and risks of employing this technique in COVID-19 patients. In addition, proning is a resource intensive intervention that requires a specialized skillset to initiate and maintain patients in this

position over the course of several hours. For this reason, this therapy might not be feasible at every center.

Data would suggest that the advantages of prone position would become limited after a certain level of disease progression

and fibrosis. However, there is constantly new data regarding COVID-19 patients and information continues to evolve daily. More frequently, patients are being prone while still maintaining spontaneous breathing—the results of this intervention is an area for future studies. Lastly, the use of prone position in COVID-19 requires prolonged sessions that are unprecedented in the treatment of ARDS patients, and as such there is more to learn about its appropriate use in COVID-19 patients.

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