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Initial emergency department mechanical ventilation strategies for COVID-19 hypoxemic respiratory failure and ARDS

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging viral pathogen that causes the novel coronavirus disease of 2019 (COVID-19) and may result in hypoxemic respiratory failure necessitating invasive mechanical ventilation in the most severe cases.
Objective: This narrative review provides evidence-based recommendations for the treatment of COVID-19 related respiratory failure requiring invasive mechanical ventilation.
Discussion: In severe cases, COVID-19 leads to hypoxemic respiratory failure that may meet criteria for acute respiratory distress syndrome (ARDS). The mainstay of treatment for ARDS includes a lung protective ventilation strategy with low tidal volumes (4–8 mL/kg predicted body weight), adequate positive end-expiratory pressure (PEEP), and maintaining a plateau pressure of $\leq$30 cm H_2O. While further COVID-19 specific studies are needed, current management should focus on supportive care, preventing further lung injury from mechanical ventilation, and treating the underlying cause.
Conclusions: This review provides evidence-based recommendations for the treatment of COVID-19 related respiratory failure requiring invasive mechanical ventilation.

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1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging viral pathogen that causes mild illness in some while others progress to respiratory failure requiring invasive mechanical ventilation [1,2]. The disease caused by SARS-CoV-2 has been termed the novel coronavirus disease of 2019 (COVID-19) [3]. Though incidence data are limited, a large case series of 1300 patients with COVID-19 from Italy found that 88% of critically ill patients required mechanical ventilation [4]. The mortality of those placed on mechanical ventilation is 24.5% to 28% in case series and may be even higher as many patients still remain in the hospital [4,5]. One study conducted prior to COVID-19 suggests a lung protective strategy started in the emergency department (ED) is associated with a reduction in hospital mortality, pulmonary complications, and days requiring mechanical ventilation [6]. Therefore, it is important for emergency medicine clinicians to be aware of the management of mechanically ventilated patients, particularly as these patients may be boarding in the ED for an extended period of time.

In the severest form, the characteristics of COVID-19 related respiratory failure may meet the definition of acute respiratory distress syndrome (ARDS) [7-10]. ARDS is defined by the Berlin criteria (Table 1) [11] and exists on a spectrum as a heterogeneous syndrome caused by multiple etiologies [12,13]. Practice guidelines from the Surviving Sepsis Campaign and National Institutes of Health (NIH) on the management of COVID-19 recommend a lung protective strategy with a high positive end-expiratory pressure (PEEP) strategy and low tidal volumes (4–8 mL/kg predicted body weight) [14-16]. This review will discuss the physiology underlying COVID-19 related ARDS, lung protective ventilation strategies, individualized approaches to mechanical ventilation, additional therapies, and a recommended approach to mechanical ventilation for the emergency clinician.

2. Methods

This is a narrative review of invasive mechanical ventilation strategies for COVID-19 related respiratory failure. Authors conducted a literature review of PubMed and Google Scholar using keywords of "ARDS" OR "Acute Respiratory Distress Syndrome" OR "COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" OR "hypoxemic respiratory failure" OR

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Table 1
The Berlin definition of the acute respiratory distress syndrome [11].

Clinical Feature	Definition
Timing	Develops within one week of clinical insult
Chest Imaging	Bilateral opacities not otherwise explained by pleural effusions, lobar collapse, or nodules
Origin of Edema	Non-cardiogenic edema; edema not suspected to be from an elevated left atrial pressure causing hydrostatic edema; an echocardiogram may be needed in unclear cases
Oxygenation	Mild: PaO_2/FiO_2 of >200 mm Hg to ≤300 mm Hg with PEEP or CPAP ≥5 cmH_2O Moderate: PaO_2/FiO_2 of >100 mm Hg to ≤200 mm Hg with PEEP ≥5 cmH_2O Severe: PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥5 cmH_2O

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; CPAP, continuous positive airway pressure.

"mechanical ventilation" OR "driving pressure" OR "ventilator-induced lung injury" from 1994 to May 2020. Respiratory physiology studies from 1969 to 1994 were also included. Authors evaluated case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, and other narrative reviews. Authors also reviewed guidelines and supporting citations of included articles. Authors decided which studies to include for the review by consensus. When available, systematic reviews and meta-analyses were preferentially selected. These were followed sequentially by randomized controlled trials, prospective studies, retrospective studies, case reports, and other narrative reviews when alternate data were not available. Case reports, case controls, cohort studies, randomized clinical trials, meta-analyses and systematic reviews, and narrative reviews were included. Authors decided on the inclusion of 119 studies and included a total of 20 systematic reviews and meta-analyses, 30 randomized controlled trials, 8 prospective studies, 12 retrospective studies, 3 basic science experimental studies, 11 case reports or case series, 22 narrative reviews and 13 expert consensus documents and guidelines.

3. Discussion

3.1. Pathophysiology of acute respiratory distress syndrome and COVID-19

Acute respiratory distress syndrome is a complex and heterogeneous syndrome [11,17]. Causes of ARDS include non-infectious etiologies (e.g., trauma, pancreatitis), pulmonary infections, and non-pulmonary infections [12,17]. However, the common theme is an inflammatory response causing lung and systemic organ injury. A severe, hyperinflammatory, cytokine-mediated lung injury has also been implicated in COVID-19 [9,18]. Pro-inflammatory cytokines may interfere with the normal adaptive response of hypoxic vasoconstriction [19]. Damage to alveolar epithelium and endothelium leads to leakage of protein-rich fluid and non-cardiogenic pulmonary edema [17]. Consequently, the injured lung becomes at greater risk of atelectasis with impairment of surfactant, alveolar edema and hemorrhage, reduced lung compliance, increased ventilation-perfusion mismatching, and right-to-left shunting [17,20]. All of these factors contribute to hypoxemia. The histological characteristic of ARDS is diffuse alveolar damage, though interestingly this finding is not observed in all patients meeting the Berlin definition of ARDS [17]. This pattern of diffuse alveolar damage has also been noted in an autopsy case series of COVID-19 patients [19,21].

ARDS is a clinical diagnosis that relies on the 2012 Berlin definition (Table 1) [11]. Notably, ARDS is defined as an acute process with bilateral lung opacities on imaging not from cardiogenic edema and a partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) ratio of ≤300 mm Hg on a positive end-expiratory pressure (PEEP) of at least 5 cm H_2O. ARDS is further categorized into mild, moderate, or severe, depending on the degree of impairment. Patients with COVID-19 requiring mechanical ventilation frequently meet the definition of ARDS [7,8].

Lung compliance in COVID-19 related respiratory failure is variable [7,22]. It is important to note that respiratory system compliance of ≤40 mL/cm H_2O was also originally considered in the Berlin definition of ARDS but was excluded after further evaluation [11]. Studies of ARDS in non-COVID-19 patients have also demonstrated a range of lung compliances and underlying causes [12,13], that are similar to currently published COVID-19 related ARDS patients [10]. This suggests that the treatments of ARDS developed over several decades remain applicable to the range of lung pathology observed in COVID-19 related respiratory failure [10,23]. Moreover, deviation from a lung protective ventilation strategy with a high V_T and low PEEP has historically been shown to cause lung injury in animal models [24-27].

Once ARDS is diagnosed, the treatment focuses on addressing the underlying cause while preventing ventilator induced lung injury (VILI) [24]. There are multiple sources of lung injury (Table 2). Volutrauma occurs from excess volume or pressure leading to overdistension (i.e. stretching) of at-risk alveoli [17,24]. Lung injury caused by overdistension may be noted grossly by barotrauma (e.g. pneumothorax, pneumomediastinum) or occur silently on the alveolar level [24]. In ARDS, the functional lung volume is reduced due to alveolar injury, edema, and atelectasis [17]. The reduction in aerated lung space is the underpinning for the low V_T of lung protective ventilation (LPV). The delivered V_T generates a pressure within the lung. The generated pressure will vary depending on the size of the V_T and an individual's respiratory system compliance [28]. The plateau pressure (P_{Plat}) estimates alveolar pressure, with a high P_{Plat} suggesting alveolar

Table 2
Types of ventilator induced lung injury (VILI) [24].

Injury	Mechanism	Minimization Strategy
Atelectrauma (Recruitment/ derecruitment injury)	Lung injury caused by cyclic opening and collapse of atelectatic, but recruitable lung units.	Ensure appropriate PEEP and tidal volumes.
Barotrauma	Lung injury (e.g. pneumothorax, pneumomediastinum, etc.) caused by high transpulmonary pressure disrupting the alveolar structures.	Minimize excessive airway pressure and tidal volumes.
Biotrauma	Mechanical lung injury causes up-regulation and release of cytokines with a subsequent pulmonary and systemic inflammatory response causing multi-organ dysfunction.	Lung protective strategy while treating the underlying cause. Consider immunomodulating therapies (e.g. corticosteroids).
Oxygen toxicity	Injury caused by the inability of cells to overcome oxygen free radicals, and absorption atelectasis.	Turn down FiO_2 as soon as possible to target an oxygen saturation of 92–96%.
Patient self-inflicted lung injury (P-SILI)	Intense inspiratory force by the patient causing high transpulmonary pressure swings.	Increase sedation with or without neuromuscular blockade if persistent, excessive, spontaneous respiratory effort is present.
Shearing injury	High shear forces at the junction of the collapsed and open lung units causing lung injury.	Use appropriate PEEP to maintain recruitment and low tidal volumes. Modes like airway pressure release ventilation (APRV) may reduce shear stress.
Volutrauma	Non-homogenous lung injury caused by alveolar overdistension.	Ensure a low tidal volume of 4–8 mL/kg PBW.

overdistension [24,28]. Though a specific safe pressure threshold is unknown, it is recommended to maintain a $P_{Plat} < 30$ cmH_2O and a driving pressure (P_{Plat} – PEEP) < 15 cm H_2O [6,12,29]. The P_{Plat} is measured with a 0.5-second pause at the end of inspiration in a passive patient when inspiratory flow reaches zero (Fig. 1) [12]. It is important the patient is passive (i.e. without any spontaneous respiratory effort) during the inspiratory hold, as any patient effort (e.g. expiratory or inspiratory effort) will distort the P_{Plat} measurement. Additional injury may come in the form of *atelectrauma*—repetitive opening and closing of alveoli leading to alveolar injury and denaturing of surfactant [17,24]. Atelectrauma has been shown to increase inflammatory markers in animal models [12,17,25-27]. Atelectrauma is minimized by using appropriate PEEP to maintain alveolar aeration (i.e. recruitment) throughout the respiratory cycle [24].

3.2. A lung protective strategy

In COVID-19 related respiratory failure, care is focused on maintaining oxygenation while preventing VILI with lung protective ventilation (LPV). The mainstays of LPV are low V_T, sufficient PEEP to maintain lung recruitment, and low airway pressures [17,30-34]. Though ARDS is a heterogeneous syndrome, the following is recommended for all ARDS patients: (1) V_T of 4 to 8 mL/kg predicted body weight (PBW) and (2) targeting a P_{Plat} < 30 cm H_2O (Tables 3 and 4) [15,34,35]. Emerging data from several American tertiary care centers support this approach in patients with COVID-19 requiring invasive mechanical ventilation [10].

The ARDSnet ARMA trial showed a mortality benefit in patients with ARDS using a low (6 mL/kg PBW), as compared to a high (12 mL/kg PBW), V_T ventilation strategy, PEEP set by the lower PEEP/FiO_2 table (Table 4) and a goal P_{Plat} less than 30 cm H_2O (Table 3) [12]. Though an initial improvement in oxygenation with a larger, 12 mL/kg V_T may be seen, this trial showed the initial improvement in oxygenation with a larger V_T is at the expense of a later increase in mortality [12]. Early initiation of LPV initiated in the ED is associated with improved mortality and patient outcomes [6]. The traditional LPV approach uses a PEEP/FiO_2 table to determine the set PEEP based on the degree of hypoxemia and FiO_2 requirement (Table 4) [12]. Currently, the Surviving Sepsis Campaign and NIH recommend a higher PEEP strategy over lower PEEP strategy for patients with ARDS due to COVID-19; however, this is a weak recommendation based on low-quality evidence [14-16,36]. This prescriptive setting of PEEP has been criticized in COVID-19 because it lacks sufficient individualization to the variable response to PEEP [37].

3.3. An individualized approach

3.3.1. Description of PEEP and recruitment maneuvers in ARDS

The tenants of ARDS management and LPV are low Vt and cautious use of PEEP [17]. ARDS is a heterogeneous disease with a variety of potentially recruitable, PEEP-responsive lung units [38]. This heterogeneity means a single prescribed V_T and PEEP impacts each lung unit differently depending on the local level of functional impairment (e.g. edema, atelectasis). An inherent tradeoff with any PEEP application is the need to balance improving oxygenation with potentially inducing VILI [39,40]. PEEP can be beneficial by recruiting and aerating collapsed lung units, improving gas exchange, and minimizing atelectrauma. However, it can also be harmful by over-distending the lung, increasing pulmonary vascular resistance, worsening ventilation and perfusion matching, and inducing hemodynamic instability by decreasing cardiovascular preload. Finding the optimal PEEP may not rest on one variable [22]. The elusive goal to find the optimal PEEP is not new [41] and

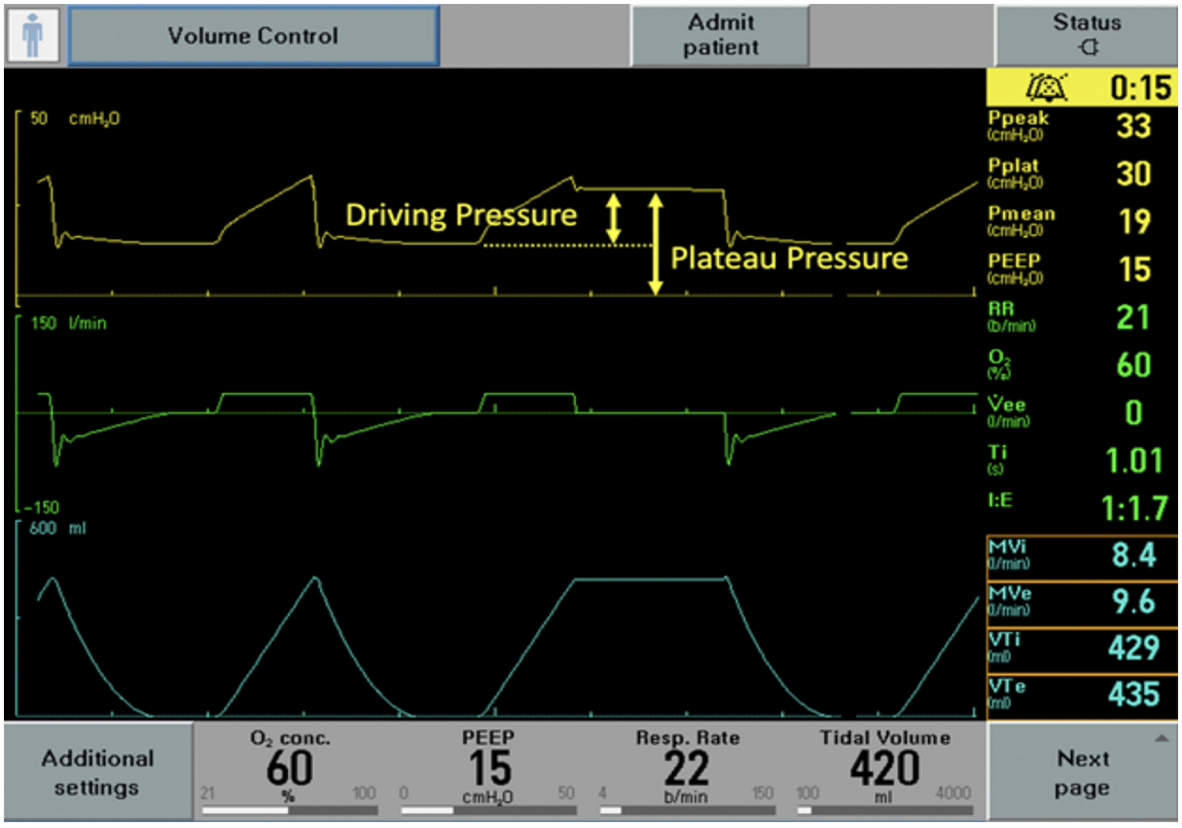

Fig. 1. An example of a plateau pressure, checked after an end inspiratory pause when inspiratory flow has reached zero. The plateau pressure is 30 cm H_2O, in a volume control mode with a set 420 mL (6 mL/kg PBW) tidal volume. The driving pressure is 15 cm H_2O (plateau pressure of 30 cm H_2O - PEEP of 15 cm H_2O). The driving pressure is related to the static compliance of the respiratory system (C_{RS}) by C_{RS} = Tidal Volume/Driving Pressure. In this patient the C_{RS} is low at 28 mL/cm H_2O.

Table 3
The conventional lung protective ventilation strategy [12].

Variable	Setting
Tidal Volume	6 mL/kg PBW (Range: 4–8 mL/kg PBW)
Plateau pressure	Less than 30 cm H_2O
Respiratory rate	Up to 35 breaths per minute, goal of pH 7.30–7.45 but may allow permissive hypercapnia with a pH >7.15
Positive End Expiratory Pressure	Initiate at ≥5 cm H_2O Titrate according to ARDSnet lower PEEP/higher FiO_2 table
Oxygenation target	Titrate FiO_2 to:
PaO_2	55–80 mmHg
SpO_2	88–95%

Abbreviations: PBW (predicted body weight), PEEP (positive end-expiratory pressure).

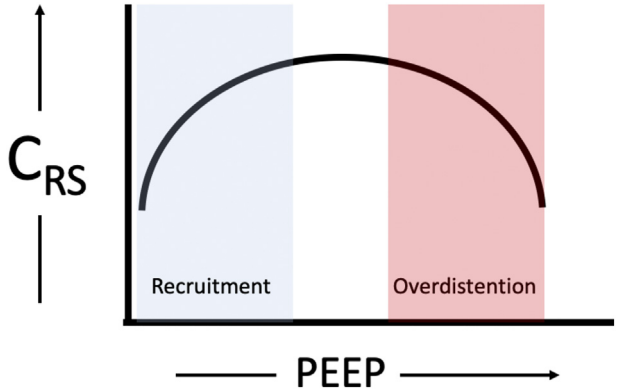

Fig. 2. A representation of the relationship between compliance of the respiratory system (C_{RS}) and PEEP. If increasing PEEP improves recruitment, by aeration of previously non-aerated lung, then compliance will improve until the lungs are overdistended and compliance worsens.

strives to maximize the beneficial effects of PEEP while minimizing any potential harmful effects.

One method of PEEP adjustment was described in the ARDSnet trial in the form of a high and low PEEP/FiO_2 table based on levels of hypoxemia [12] (Table 4). A mortality benefit has not been detected with the high PEEP/FiO_2 compared to the low PEEP/FiO_2 table [42-45]. Despite lack of proven superiority, current recommendations support a high PEEP strategy for moderate to severe ARDS ($PaO_2/FiO_2 \leq 200$ mm Hg) which is consistent with current COVID-19 recommendations [14-16,34,36,46]. The PEEP tables are unable to take into account the extent of individual lung injury and recruitability. For instance, a low PEEP in potentially recruitable lungs does not allow for the beneficial effects of PEEP while a high PEEP strategy with low lung recruitability can lead to over-distention and increased lung injury [47]. Marini and Gattinoni [37] suggest that different COVID-19 ARDS phenotypes require varied management strategies. These two "H" and "L" phenotypes are based on lung CT imaging, compliance, and response to PEEP [22,37,48,49]. However, these phenotypes for COVID-19 have not been validated in other studies and should not form the foundation of therapy. ARDS phenotypes have been previously described [50] and may provide insight into a personalized approach. Personalized ventilator strategies compared to a uniform approach may be helpful; however, caution must be used with personalization because if incorrectly assessed, mortality may increase [51].

There remains controversy surrounding the use of recruitment maneuvers. A recruitment maneuver is a prolonged inspiratory hold on higher levels of CPAP, such as 35–40 cm H_2O for 30–40 s [16,52]. Evidence from a systematic review and meta-analysis showed improved oxygenation without an increased risk of barotrauma [52]. However, other studies show recruitment maneuvers with PEEP titration increase mortality compared to a standard PEEP/FIO_2 table [53]. In COVID-19, if hypoxemia exists despite optimization of ventilator settings, recruitment maneuvers may be considered while monitoring for harmful effects such as oxygen desaturation, hypotension, or barotrauma [15,16].

3.3.2. Driving pressure

Driving pressure can be calculated easily at the bedside by obtaining the P_{Plat} during an end-inspiratory pause in a passive patient in a volume-targeted mode of ventilation. It is calculated by P_{Plat} - PEEP. The driving pressure reflects the static compliance of the respiratory system (C_{RS}) by the equation of $C_{RS} = V_T / (P_{Plat} - PEEP)$. As the equation suggests, a change in V_T or a change in pressure will affect the compliance of the respiratory system. It is possible that a change in PEEP may decrease the pressure associated with a V_T (i.e. improve the C_{RS}) if it is able to recruit previously non-aerated lung (Fig. 2) [29,54]. Similarly, it is also possible that an increase in PEEP could worsen C_{RS} if an increase in pressure does not improve recruitment and instead causes overdistension (Fig. 2), leading to lung injury and worsening dead space or causing hemodynamic compromise [55]. The driving pressure may offer a better quantification of functional lung size as compared to PBW for a set V_T because PBW is proportional to total lung size and not the reduced, functional lung size in ARDS [51,55].

Amato et. al. performed a retrospective review [29] of the ARDSnet trial data and showed that driving pressure was the ventilation variable that best stratified mortality risk in ARDS. Higher mortality was noted with a higher P_{Plat} only when higher driving pressures were present. Similarly, protective effects of PEEP were noted only when associated with decreased driving pressures [29]. The association of higher driving pressures and higher mortality rate for mechanically ventilated patients with ARDS was also identified in a subsequent meta-analysis. Despite the strong association with mortality in retrospective studies [29,56], the routine use of driving pressure in ARDS has not demonstrated a mortality benefit in prospective randomized controlled trials [53,56]. One study using recruitment maneuvers followed by PEEP titration to the best C_{RS} demonstrated an increase in mortality when compared to PEEP set by the low PEEP/FiO2 table [53]. This study suggests the combination of recruitment maneuvers and PEEP titration to best C_{RS} should not be used together to set PEEP. Therefore, the driving pressure should be used as a complement—not a replacement—to the evidence-based V_T, P_{Plat}, and PEEP recommendations.

When ventilating an ED patient in a volume targeted mode, clinicians should re-evaluate the ventilator settings if the driving pressure is above 15 cm H_20 [29]. The first option to decrease the driving pressure

Table 4
PEEP/FiO_2 titration strategies [12].

Lower PEEP/FiO_2 Combination														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP (cm H_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
Higher PEEP/FiO_2 Combination														
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5	0.6	0.7	0.8	0.8	0.9	1.0	
PEEP (cm H_2O)	5–12	14	14	16	16	18	20	20	20	20	22	22	22–24	

Abbreviations: PEEP (positive end-expiratory pressure), FiO_2 (fraction of inspired oxygen).

is to decrease the V_T. Once a V_T of ≤4–6 mL/kg PBW has been achieved, the next step is to adjust the PEEP and follow the change in driving pressure. At a fixed V_T, the PEEP that leads to the smallest driving pressure is the ideal PEEP for improving respiratory system compliance (Fig. 2). This is accomplished by incrementally adjusting PEEP, to the range of the targeted PEEP from the PEEP/FiO_2 table (Table 4), while monitoring the driving pressure. The goal of assessing driving pressure is to detect the individual heterogeneity of PEEP responsiveness seen in COVID-19 related ARDS. Driving pressure may aid in identifying those who may benefit, or be harmed, from a higher or lower PEEP than prescribed in the PEEP/FIO_2 tables.

3.3.3. Transpulmonary pressure

Regional lung overdistention is a key factor in VILI, but it can be difficult to measure directly [24]. Overdistention occurs because of the high-pressure differences across the lung tissue, referred to as the transpulmonary pressure. The P_{Plat} is the average alveolar pressure and often serves as a surrogate for inflation pressure and overdistention. In some instances, a high alveolar pressure (i.e. P_{Plat} >30 cm H_2O) may not reflect an injurious high transpulmonary pressure because of the counter-pressure (i.e. pleural pressure) provided by the chest wall and abdominal contents. As an example, a trumpet player with a very high alveolar pressure does not encounter elevated transpulmonary pressures because of the elevated pleural pressures generated to play the instrument [24,57]. Similarly, a stiff chest wall or rigid abdominal compartment may cause a high P_{Plat} despite a safe, normal transpulmonary pressure [24]. One method of estimating pleural pressure is by using a balloon manometer to measure the esophageal pressures as a surrogate for pleural pressure. However, this complex strategy is not recommended in the emergency department as it is cumbersome and has not been shown to be beneficial when compared to empiric PEEP set by the PEEP/FiO_2 tables (Table 4) [58,59].

3.4. Additional therapies in ARDS

3.4.1. Prone positioning

Prone positioning has been utilized for many years to improve oxygenation and outcomes in ARDS [60,61]. This position, commonly referred to as "proning," utilizes gravitational effects to conform the shape of the lung to the chest cavity and ultimately reduce the pleural pressure gradient from non-dependent to dependent regions [62]. In addition to a more favorable and equitable distribution of aeration, proning increases end-expiratory lung volume, improves ventilation-perfusion matching, increases secretion clearance, and alters chest wall mechanics, leading to regional changes and improvements in overall lung ventilation [61,63-65]. Prone positioning has been shown in several studies to protect against VILI [62,66-69] and also has a mortality benefit [60,70,71]. Proning should be considered in patients with ARDS and a PaO_2/FiO_2 ratio < 150 despite optimized ventilator settings [60]. This is consistent with the current COVID-19 recommendations where patients with moderate to severe ARDS may be proned for 12 to 16 h at a time [16]. Proning on mechanical ventilation is beneficial when started early, after 12–24 h of stabilization on the ventilator [60]. Unless there is a significant delay in the transfer, proning in the mechanically ventilated patient can generally wait for admission to the intensive care unit (ICU). If proning is started in the ED, neck and shoulder mobility should be assessed to ensure the patient can tolerate a prone position. Additionally, the team must wear appropriate PPE [15] and must be trained to monitor for pressure points and avoid accidental extubation, which can lead to loss of recruitment and potential exposure to the team. Due to the inherent risks and challenges, a collaborative approach with a practiced team is recommended prior to attempting prone positioning in the emergency department for the mechanically ventilated patient.

3.4.2. Inhaled pulmonary vasodilators

Inhaled pulmonary vasodilators predominantly distribute to ventilated alveoli causing localized vasodilation, thereby improving ventilation-perfusion matching [72-74]. While no mortality benefit has been demonstrated [75-77], inhaled nitric oxide and inhaled prostacyclins (e.g. epoprostenol) are used as rescue agents to reduce hypoxia-mediated vasoconstriction and improve oxygenation in severe ARDS [72,75,78,79]. The ease of delivery, inexpensive cost, and infrequent adverse events have made prostacyclins a more favorable choice [73], as inhaled nitric oxide [80] has been associated with increased renal impairment [81]. These decisions must be made within the local practice environment accounting for availability and ventilator circuit type. Also, there may be an increased risk of aerosolization with inhaled pulmonary vasodilators that should be taken into consideration. The Surviving Sepsis Campaign guidelines for COVID-19 recommend against the use of routine use of inhaled nitric oxide but suggest that a trial of inhaled pulmonary vasodilators may be used as a rescue therapy while monitoring for rapid improvement in oxygenation [16].

3.4.3. Neuromuscular blocking agents (NMBA)

Long-acting neuromuscular blocking agents (e.g. vecuronium and cisatracurium) used in moderate-to-severe ARDS have been shown to minimize patient-ventilator dyssynchrony, decrease work of breathing [82], improve oxygenation [83], reduce inflammatory biomarkers [84], and potentially increase the number of ventilator-free days and days outside the ICU [85]. The routine use of neuromuscular blockade in ARDS has been called into question after a 2019 multicenter randomized control trial evaluating the use of early paralytics and high PEEP in patients with moderate-to-severe ARDS found no difference in 90-day mortality when compared to usual therapy [86]. The evidence on neuromuscular use in COVID-19 induced ARDS is limited, and the long-term outcomes are unclear. In mechanically ventilated COVID-19 patients with moderate-to-severe ARDS, the Surviving Sepsis Campaign guidelines suggest using intermittent NMBA boluses instead of a continuous infusion to better facilitate lung protective ventilation [16]. The use of continuous NMBA infusions for up to 48 h should be reserved for patients with persistently high P_{Plat}, poor oxygenation, and ventilator dyssynchrony [16].

3.4.4. Medications

The role of corticosteroids in the early and late stages of ARDS is controversial and widely debated. Two meta-analyses demonstrated reduced mortality, increased ventilator-free days, and accelerated resolution of disease when steroids were started several days after the onset of ARDS [87,88]. A more recent trial examining dexamethasone in patients with ARDS and a PaO_2/FiO_2 ratio of <200 mmHg despite optimal ventilator settings suggested an improvement in outcomes [89]. However, a different meta-analysis did not support their use in either the acute or later fibroproliferative phases of the disease [90]. The current evidence of steroids use in COVID-19 induced ARDS is still emerging. A non-peer reviewed study of 26 patients with severe COVID-19 reported a decreased requirement for supplemental oxygenation and improvement on radiological chest imaging among patients who received corticosteroids [91]. There is a randomized control trial in Chongqing, China actively enrolling patients looking at the effect of glucocorticoids in COVID-19 patients with severe disease, which may provide further data [92]. Two more recent retrospective studies, albeit with small sample sizes and poor data controllability, reported that low-dose corticosteroid therapy may not delay viral clearance in COVID-19 patients [93,94]. Based on several Cochrane reviews on the use of steroids in viral pneumonia and a retrospective cohort study of patients with COVID-19 pneumonia [95], the Surviving Sepsis Campaign guidelines suggest the use of corticosteroids in critically ill patients with COVID-19 induced ARDS [16], while the NIH guidelines [15] make no recommendations based on limited evidence. Given the small improvements in mortality and faster resolution of septic shock observed from

recent systematic reviews [96,97], they advise against the use of systemic corticosteroids of COVID-19 patients without ARDS unless the patient is in septic shock [16]. In patients with COVID-19, meeting criteria for ARDS, steroids should be considered in consultation with the admitting critical care team.

3.4.5. Venovenous extracorporeal membrane oxygenation

Venovenous extracorporeal membrane oxygenation (vvECMO) is a form of pulmonary bypass that uses an external membrane to allow for oxygen diffusion into the blood and the diffusion of carbon dioxide out of the blood. Over the last decade, several trials have shown increased use and potential benefits of vvECMO in severe ARDS when conventional ARDS management failed [98,99]. In COVID-19 patients, the Extracorporeal Life Support Organization (ELSO) guidelines state that indications for vvECMO should not differ from their usual recommendations or other existing guidelines [100,101]. The Surviving Sepsis Campaign guidelines for COVID-19 and ELSO recommend transfer to an ECMO experienced center for patients with severe ARDS and refractory hypoxemia despite maximal ARDS therapies [16].

3.5. An initial approach to COVID-19 hypoxemic respiratory failure

It is difficult to identify the optimal management of COVID-19 hypoxemic respiratory failure. Herein, we provide a rational approach based on the currently available evidence and lessons learned over the last few decades (Fig. 3). An initial approach to manage hypoxemia includes a trial of simple oxygen devices, high-flow nasal cannula (HFNC), or non-invasive positive pressure ventilation (NIPPV) if HFNC is not available [16]. A trial of HFNC or non-invasive positive pressure (NIPPV) is reasonable if intubation is not immediately indicated, if conventional oxygen devices fail to maintain an oxygen saturation of >90%, or if increased respiratory effort persists. HFNC has shown particular success in prior studies of hypoxemic respiratory failure and should be considered as a first-line treatment when simple oxygen devices fail to correct the hypoxemia [14-16,102]. Non-invasive positive pressure (NIPPV) delivering PEEP in the form of continuous positive airway pressure (CPAP) may also have advantages, particularly with a helmet interface [103]. Bilevel positive pressure settings, delivering an additional inspiratory pressure, risk delivering injurious V_T [102] and should be avoided unless otherwise indicated (e.g. an exacerbation of obstructive lung disease) [104]. The addition of awake, self-prone positioning or repositioning may improve oxygenation in patients with COVID-19 [105], but long-term effects of this practice are unclear. Personal protective equipment and airborne precautions must be utilized when using devices that can cause aerosolization [15]. The risks of aerosolization may not be increased with HFNC as compared to low flow oxygen devices [106]; if HFNC is used, a surgical mask to cover the device on the patient's face is recommended.

When HFNC or NIPPV is started, patients must be reassessed frequently—waiting until failure is associated with worse outcomes [102,107,108]. Patients on HFNC who remain tachypneic, have significant work of breathing, have rapidly escalating oxygen requirements, or remain hypoxic despite maximal flow (i.e. 60 L/min) and FiO_2 should be intubated. The severity of hypoxemia, underlying illness, and clinical trajectory of these patients are important components of the decision to intubate. NIPPV failure rates for acute hypoxemic respiratory failure are higher in patients with pneumonia, sepsis, severe hypoxemia ($PaO_2/FiO_2 \leq$ 150–200 mm Hg) [109,110], and persistently large tidal volumes (>9.5 mL/kg PBW) [111]. In those with persistently high respiratory effort, one must consider the possibility of self-inflicted lung injury. It is theorized that patients with a high respiratory effort are generating very high V_T and high transpulmonary pressure, which could potentially lead to a self-inflicted lung injury [37,112]. Patients with persistently high respiratory efforts despite non-invasive support measures may benefit from early intubation, sedation, and control of V_T and airway pressure.

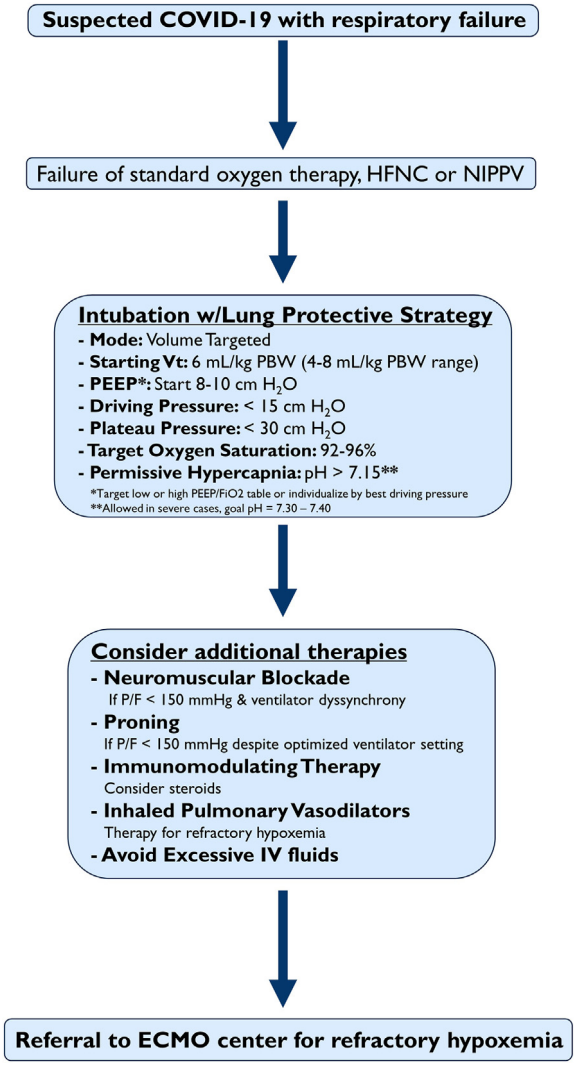

Fig. 3. A recommended initial approach to COVID-19 related hypoxemic respiratory failure in the Emergency Department. Abbreviations: HFNC (high flow nasal cannula), NIPPV (non-invasive positive pressure ventilation), PBW (predicted body weight), V_T (tidal volume), P/F (PaO_2/FiO_2 ratio), IV (intravenous)

Once invasive mechanical ventilation has started, LPV with low V_T and appropriate PEEP should be started (Fig. 3 and Table 4). This strategy has been successfully used in a case series of COVID-19 patients [10] and is recommended by The Surviving Sepsis Campaign and NIH guidelines [14-16]. Ventilator modes vary between institution and device. A simple and effective strategy for the emergency department is to choose a volume targeted mode of ventilation (e.g. volume control). This allows for a safe, prescribed V_T to be delivered. A pressure targeted mode (e.g. pressure control) is also an option but the delivered V_T is less strict and will vary depending on the patient's lung compliance, resistance, and the set inspiratory time. There is no outcome evidence to support the superiority of a pressure-controlled or volume-controlled mode of ventilation in ARDS [113]. Airway pressure release ventilation (APRV) has been used in ARDS [114] but the mode is complex, not available on every ventilator, and can lead to significant adverse events if used improperly [115]. For these reasons, APRV is not the initial preferred strategy in the ED, but this may vary by institution or local practice. Choosing a volume-controlled mode that allows a set V_T is recommended. When the volume is set, the P_{Plat} should be monitored by an end-inspiratory pause to ensure it remains < 30 cm H_2O. Similarly, the driving pressure should be targeted < 15 cm H_2O. If the P_{Plat} or driving pressure are above these targets, decrease the V_T by

1 mL/kg to a minimum of 4 mL/kg. The respiratory rate may need to be increased up to 35/min to maintain an appropriate minute ventilation. A pH target of 7.30–7.45 is recommended, but if necessary, permissive hypercapnia may be instituted, tolerating a pH $\geq$ 7.15 [12].

Ideally, sedation should be kept as light as possible with a Richmond Agitation Sedation Scale of 0 (alert and calm) to −1 (drowsy but awakens to voice for >10 s); a lighter sedation strategy started in the ED is associated with improved outcomes [116]. Ventilator dyssynchrony is common [117] and places patients at risk for lung injury. A potential treatment for ventilator dyssynchrony is liberating the V_T up to 8 mL/kg, if the P_{Plat} and driving pressure are at safe levels, or adjusting the inspiratory flow pattern. If the P_{Plat} or driving pressure is elevated or dyssynchrony persists, deep sedation with or without NMBAs may be needed.

Adjust the FiO_2 to target an oxygen saturation of 92–96% [16]. The change from the original ARDS trial target of 88–95% [12] reflects a 2020 multicenter, randomized trial demonstrating a lack of benefit and potential of harm with a conservative (88–92%) vs. liberal ($\geq$96%) oxygenation strategy in ARDS [118]. The response to PEEP will be variable for all patients [38]. The PEEP/FiO_2 tables (Table 4) provide guidance and have been used successfully in ARDS [12]. After intubation, start with a PEEP of 8–10 cm H_20 and choose the range of PEEP by the high or low PEEP/FiO_2 table (Table 4) [6]. Adjust the PEEP every 15 min by 2–3 cm H_2O, while monitoring the P_{Plat}, driving pressure, blood pressure, and pulse oximetry after each adjustment. A P_{Plat} <30 cmH_20 and driving pressure <15 cmH_20 should be targeted. If pressures are above these levels, patients are at risk for VILI.

A conservative fluid resuscitation strategy should be used in patients with ARDS, as this may improve lung function [14,16,119]. Adjunctive therapies such as pulmonary vasodilators, corticosteroids, and proning should be considered on a case by case basis with input from the admitting critical care team. If the patient is unable to be oxygenated or ventilated despite optimized ventilator settings, consultation with an ECMO center should be considered.

4. Conclusion

In severe cases, COVID-19 leads to hypoxemic respiratory failure that may meet criteria for ARDS. While further COVID-19 specific studies are needed, the mainstay of treatment for COVID-19 related ARDS remains the early implementation, in the ED, of a lung protective ventilation strategy with low tidal volumes, adequate PEEP, and maintaining a plateau pressure of <30 cm H_2O. Adjunctive therapies such as corticosteroids, proning, NMBAs, pulmonary vasodilators, and ECMO in refractory cases should be considered on a case by case basis with input from the admitting critical care team.

Declaration of Competing Interest

None.

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