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INFECTIOUS DISEASE (J GLAUSER, SECTION EDITOR)

Managing Severe Hypoxic Respiratory Failure in COVID-19

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Abstract

Purpose of Review Adult respiratory distress syndrome is a life-threatening complication from severe COVID-19 infection resulting in severe hypoxic respiratory failure. Strategies at improving oxygenation have evolved over the course of the pandemic.

Recent Findings Although non-invasive respiratory support reduces the need for intubation, a significant number of patients with COVID-19 progress to invasive mechanical ventilation. Once intubated, a lung protective ventilation strategy should be employed that limits tidal volumes to 6 ml/kg of predicted body weight and employs sufficient positive end-expiratory pressure to maximize oxygen delivery while minimizing the fraction of inspired oxygen. Intermittent prone positioning is effective at improving survival, and there is a growing body of evidence that it can be safely performed in spontaneously breathing patients to reduce the need for invasive mechanical ventilation. Inhaled pulmonary vasodilators have not been shown to improve survival or cost-effectiveness in COVID-19 and should be used selectively.

Summary Finally, the best outcomes are likely achieved at centers with experience at severe ARDS management and protocols for escalation of care.

Keywords COVID-19 · Acute respiratory distress syndrome · Hypoxia · Intubation · Mechanical ventilation · Lung protective ventilation

Introduction

The global pandemic caused by SARS CoV-2 has resulted in more than 250 million worldwide cases of COVID-19 and more than 5 million deaths [1]. Although most patients with COVID-19 experience mild symptoms, up to 35% have severe disease that requires supplemental oxygen, and up to 20% are admitted to an intensive care unit (ICU) for acute respiratory distress syndrome (ARDS) [2]. Among patients admitted to ICUs, use of advanced respiratory support such as high-flow nasal cannula (HFNC), noninvasive positive pressure ventilation (NIPPV) such as Bi-level Positive Pressure Ventilation with a mask, and invasive mechanical ventilation (IMV) varies from 18–90%. This variability is attributed to differences in resource availability, safety concerns regarding infectious aerosol generation, and heterogenous patient factors that affect clinical decision making [2, 3]. It also indicates a lack of consensus in addressing severe hypoxia from COVID-19. This review summarizes the current evidence behind methods of advanced respiratory support for severe COVID-19 as well as best practices for addressing refractory hypoxia.

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Noninvasive Respiratory Support

Alternatives to IMV for the treatment of respiratory failure have been studied for over a decade prior to the pandemic with HFNC and NIPPV emerging as the two most used modalities for noninvasive respiratory support [4•, 5, 6•]. While both can deliver nearly 100% oxygen and aid in CO_2

removal, these are achieved through different mechanisms and incur specific advantages and disadvantages for certain populations. For example, NIPPV provides ventilatory support through high inspiratory pressures that are achieved with a tight-fitting mask at the cost of impaired secretion clearance. HFNC provides less ventilatory support through washout of the anatomic dead space, but access to the face is preserved and secretion clearance is generally maintained. Thus, HFNC received widespread acceptance before the pandemic in cases of pneumonia where secretion clearance was needed [4•]. On the other hand, NIPPV was still successfully used for hypoxic and hypercarbic respiratory failure not caused by sepsis or pneumonia [5].

Despite the popularity of noninvasive respiratory support leading up to the pandemic, initial recommendations for patients with COVID-19 emphasized the need for early intubation for those escalating beyond nasal cannula oxygen. These preliminary recommendations were largely based on concerns for infectious aerosol generation from noninvasive devices as well as questions regarding their efficacy in COVID-19. This concern eventually gave way to more widespread use of noninvasive respiratory support in part due to studies demonstrating the safety of both HFNC and NIPPV in terms of aerosol dispersion and microbiological contamination [7, 8]. There was also a growing body of evidence that both HFNC and NIPPV reduce the need for intubation thereby conserving ventilator resources [9, 10••, 11••]. While neither modality has established superior outcomes in a head-to-head study in patients with COVID-19, HFNC is still preferred at most centers in patients with concomitant sepsis or bacterial pneumonia.

Patients failing non-invasive respiratory support are at risk for worse outcome if the transition to invasive mechanical ventilation is delayed [12, 13]. Approximately 20% of patients deteriorate after 48 h of NIPPV, and this is more frequent in patients with severe baseline functional impairment [12]. These patients suffer higher mortality if NIPPV is continued rather than immediately transitioned to IMV. A similar pattern is seen with HFNC where intubation after 48 h results in worse outcomes in terms of mortality, ventilator weaning, and extubation success [13]. Proposed mechanisms for this finding are respiratory muscle fatigue and cardiac dysfunction perpetuated by the increased work of breathing in patients allowed to slowly deteriorate on noninvasive respiratory support.

Various methods have been proposed to objectively identify patients failing noninvasive respiratory support for early intubation. The ROX index measures the ratio of oxygen saturation to fraction of inspired oxygen and respiratory rate (SpO_2/FiO_2/RR) to predict the need for intubation [14]. A ROX index score more than 4.88 after 12 h is associated with a low risk for intubation. ROX index values of 3.85–4.87 required close monitoring and repeat assessment, while values less than 3.85 warrant consideration for intubation [14]. Small studies in patients with COVID-19 indicate that the ROX index is predicative for deterioration but superiority to clinical gestalt is unclear, and the score has not achieved widespread acceptance [15–17]. Regardless of whether a decision tool such as the ROX index is used, providers must set a threshold for rapid transition to IMV in failing patients that leaves a physiologic reserve for intubation.

Invasive Mechanical Ventilation

Early experience with COVID-19 produced conflicting recommendations for the optimal approach to IMV based on reports of variable lung compliance at different stages of the disease [18]. However, there are no studies suggesting that the fundamentals of ventilator management in COVID-19 have changed from the ARDSNet trials conducted 20 years ago. Thus, a lung protective approach targeting a Vt of 6 cc/kg of predicted body weight (PBW, a prediction of lean body weight from height), a plateau pressure (P_{plat}) less than 30 cm H_2O, and the application positive end-expiratory pressure (PEEP) that maintains alveoli patency are standard of care in ARDS from COVID-19 [19, 20•]. Moreover, there is no evidence that a particular mode of ventilation, either pressure or volume control, results in more favorable outcomes if a protective strategy is applied.

The principle behind the lung protective ventilation is to reduce over-inflation of vulnerable alveoli, prevent cyclic opening-closing of alveoli known as atelectotrauma, and minimize the inflammatory response associated with IMV. Practically, it involves initiation of ventilation with a Vt between 6 and 8 cc/kg PBW and titrating the Vt and respiratory rate to achieve a target Vt of 6 cc/kg while maintaining sufficient minute ventilation to sustain a pH greater than 7.25 [19]. This often requires a tolerance for a certain degree of permissive hypercapnia to keep the Vt at 6 cc/kg and P_{plat} less than 30 cmH_2O. The exact amount of hypercapnia that is tolerable and its effect on outcomes are uncertain. On one hand, elevations in $PaCO_2$ are associated with favorable outcomes in ARDS when the alternative is injurious, non-protective volumes [21]. On the other hand, severe hypercapnic acidosis is associated with acute cor pulmonale and mortality among patients receiving a lung-protective Vt strategy [22]. Studies are ongoing to determine thresholds for tolerable degrees of hypercapnia in patients receiving lung-protective ventilation for ARDS. In the meantime, it is reasonable to target values for pH and $PaCO_2$ greater than 7.25 and less than 60 mmHg, respectively.

Oxygenation is achieved through the titration of PEEP and the fraction of inspired oxygen (FiO_2) to prevent extrapulmonary organ injury from hypoxia while mitigating

the risk of pulmonary oxygen toxicity. Although the mechanism of oxygen toxicity is incompletely understood, evidence suggests that it can occur at moderate FiO_2 levels (0.5–0.6) in normal lungs, and alveolar inflammation increases the susceptibility to oxygen-derived free radicals [23]. Several studies have examined the role of liberal versus conservative approaches to oxygenation in ARDS and found that both hyperoxemia and hypoxemia were associated with worse outcomes [24, 25]. Thus, an SpO_2 range of 92–97%, corresponding to a PaO_2 of 65–90 mmHg, is a reasonable target for most patients with ARDS.

Application of PEEP limits FiO_2 requirements and improves oxygenation by recruiting alveoli, augmenting functional residual capacity, and increasing oxygen solubility in blood. While an optimal PEEP setting maximizes lung compliance and oxygen delivery, titrations of PEEP are typically performed using a standard PEEP table for a given FiO_2 [26]. As was the case prior to the pandemic, there is no evidence favoring a low versus high PEEP strategy in COVID-19. Moreover, selecting a PEEP strategy involves consideration of factors such as body habitus, expected or measured transpulmonary pressure, volume of recruitable lung, and hemodynamics. Excessive PEEP results in alveolar overdistension that increases dead space and reduces cardiac output. Thus, the decision to apply a particular PEEP strategy should be tailored to individual patient characteristics so that higher PEEP is targeted to patients most likely to benefit. Patients that typically benefit from higher PEEP are those with symmetric lung disease, high pleural pressures (i.e. obesity), and left heart failure. On the other hand, patients with right heart failure, asymmetric lung disease, hypovolemia, and increased intracranial pressure often need less PEEP.

Although early ARDSNet trials focused on keeping plateau pressures (P_{plat}) less than 30 cmH_2O, this single parameter may be an overly simple approach to complex pulmonary mechanics. Instead, driving pressure, defined as the P_{plat}–PEEP, is an estimate of compliance-adjusted Vt that has garnered particular attention in ARDS. Driving pressure less than 15 cmH_2O is the variable most associated with favorable outcomes in ARDS, likely due to less alveolar stretch that is injurious to the inflamed lung [27]. Unfortunately, driving pressure can be difficult to measure in patients taking spontaneous breaths where negative pleural pressures add to the distending pressure across the alveoli. Moreover, driving pressure as a therapeutic target is currently being studied in randomized trials, so any association with favorable outcomes is currently hypothesis generating rather than a standard of care.

Airway pressure release ventilation (APRV) is an alternative mode of ventilation that inverts the respiratory cycle with prolonged periods of inspiratory high pressure coupled with brief interruptions at low pressure for CO_2 clearance [28]. The benefit is more complete alveolar recruitment, better oxygenation, and possibly a shorter duration of mechanical ventilation in small trials [28, 29]. APRV is best used in a spontaneously breathing patient and should be avoided in patients with obstructive lung disease who are at risk for incomplete exhalation. Several centers have described success with APRV in patients with COVID-19 but there are no randomized trials suggesting a mortality benefit over conventional modes of ventilation. Moreover, success with APRV may correlate with experience using the modality to the extent that it is best employed at centers familiar with its use.

Refractory Hypoxia

Various methods have been employed to improve oxygenation in severe, refractory hypoxia. Most of these modalities are expensive, labor intensive, and show the best efficacy when employed in early ARDS. Moreover, most ARDS studies are conducted at high-volume centers with significant experience at managing severe hypoxia that may not exist at smaller centers.

Inhaled pulmonary vasodilators such as nitric oxide (iNO) and epoprostenol (iEPO) garnered attention prior to the pandemic for their ability to vasodilate the pulmonary vasculature, improve ventilation-perfusion (V/Q) matching, and reduce pulmonary vascular resistance that contributes to right ventricular failure in ARDS [30]. While studies prior to the pandemic demonstrate transient improvement in oxygenation with pulmonary vasodilators, their use does not improve mortality, duration of mechanical ventilation, multiorgan failure, ICU length of stay, or quality of life [30–32]. Despite such disappointing results, iNO and iEPO continue to be used for severe ARDS due to COVID-19. Preliminary data suggests that iEPO may improve oxygenation, but neither has demonstrated an improvement in patient-centered outcomes such as mortality or duration of mechanical ventilation in COVID-19 [33]. Additional studies are needed to determine if inhaled pulmonary vasodilators may benefit certain patients with cor pulmonale from ARDS.

On the other hand, intermittent prone positioning is a technique that has demonstrated improvements in both oxygenation and mortality in ARDS. Early studies before the pandemic on prone positioning yielded conflicting results and suffered from small sample size [34, 35]. However, the Proning Severe ARDS Patients (PROSEVA) trial randomized 466 patients with severe ARDS to intermittent prone positioning for 16 h daily versus standard supine positioning and demonstrated a 16% absolute mortality reduction in the treatment group [36•]. The PROSEVA protocol called for intermittent prone positioning until a sustained improvement in oxygenation was achieved as defined by a PaO_2:FiO_2

greater than or equal to 150 mm Hg with PEEP less than or equal to 10 cm H2O and FiO_2 less than or equal to 0.6 for at least 4 h after supine repositioning [36•]. Proposed mechanisms for the observed benefits are alveolar recruitment that improves ventilation-perfusion matching, less atelectotrauma, and improved secretion clearance. Contraindications to prone positioning include facial trauma, increased intracranial pressure, severe hemodynamic instability, and hemoptysis. Of note, all patients in the PROSEVA trial were enrolled within 36 h of intubation and the effectiveness of prone positioning in late ARDS remains unclear.

Studies on the use of prone positioning in COVID-19 are limited by small sample size and heterogenous outcomes but demonstrate favorable outcomes with respect to oxygenation and mortality [37, 38••, 39••]. These benefits have been extended to awake patients with COVID-19 receiving HFNC respiratory support and result in reduced need for intubation [40]. Patients were encouraged to lie in the prone position for as long as possible, and treatment success was associated with longer durations of prone positioning.

Unfortunately, intermittent prone positioning carries some risks and is best accomplished using institutional protocols and trained personnel. Risks associated with prone positioning include device dislodgement, hemodynamic instability, and poor access to vital structures in the event of deterioration. It is unclear if centers unfamiliar with prone positioning experience more complications than what is reported in the PROSEVA trial.

Conclusion

Severe hypoxia from COVID-19 poses unique challenges that may strain healthcare resources. Optimal care for patients with severe lung injury typically begins with noninvasive methods of oxygen delivery such as HFNC. Early identification of patients failing noninvasive support and prompt transition to IMV is needed to prevent poor outcomes. Once intubated, patients should receive a lung protective ventilation approach that targets SpO_2 between 94 and 97%. Finally, prone positioning is an effective and inexpensive means to improve mortality in eligible patients with refractory hypoxia.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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