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High-Frequency Oscillatory Ventilation for Refractory Hypoxemia in Severe COVID-19 Pneumonia: A Small Case Series

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Case series

Patients: Female, 21-year-old • Female, 53-year-old • Male, 38-year-old

Final Diagnosis: ARDS • COVID pneumonia

Symptoms: Respiratory failure • sepsis • shock

Medication: —

Clinical Procedure: High-frequency oscillatory ventilation (HFOV) • mechanical ventilation • oscillator

Specialty: Critical Care Medicine

Objective: Unusual clinical course

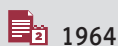
Background: COVID-19 continues to place a tremendous burden on the healthcare system, with most deaths resulting from respiratory failure. Management strategies have varied, but the mortality rate for mechanically ventilated patients remains high. Conventional management with ARDSnet ventilation can improve outcomes but alternative and adjunct treatments continue to be explored. High-frequency oscillatory ventilation (HFOV), a modality now rarely used in adult critical care medicine, may offer an alternative treatment option by maximizing lung protection and limiting oxygen toxicity in critically ill patients failing conventional ventilator strategies.

Case Reports: We present 3 patients with severe acute respiratory distress syndrome (ARDS) and sepsis due to COVID-19 who all improved clinically after transitioning from conventional ventilation to HFOV. Two patients developed refractory hypoxemia with hemodynamic instability and multiple organ failure requiring vasopressor support and renal replacement therapy. After failing to improve with all available therapies, both patients stabilized and ultimately improved after being placed on HFOV. The third patient developed severe volutrauma/barotrauma despite extreme lung protection and ARDSnet ventilation. He showed improvement in oxygenation and signs of lung trauma slowly improved after initiating HFOV. All 3 patients were ultimately liberated from mechanical ventilation and discharged from the hospital to return to functional independence.

Conclusions: Our experience suggests that HFOV offers advantages in the management of certain critically ill patients with ARDS due to COVID-19 pneumonia and might be considered in cases refractory to standard management strategies.

Keywords: Adult Multisystem Inflammatory Disease, COVID-19 Related • Respiration, Artificial • Respiratory Distress Syndrome

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/936651>



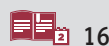
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Background

Two years into a global pandemic, COVID-19 continues to place a tremendous burden on the healthcare system, with critical disease most commonly presenting as respiratory failure. While management of hypoxemic patients remains somewhat inconsistent and controversial, most guidelines recommend management according to well-established ARDSnet guidelines [1]. The true pathophysiology of lung injury due to SARS-CoV-2 infection remains uncertain, but lung protection from oxygen toxicity and excessive tidal volumes remain important management strategies. Prone ventilation, combined with lung protective ventilation, has proven to be clinically efficacious for acute respiratory distress syndrome (ARDS) [2] and has become routine in COVID-19-associated lung injury [3]. Despite these measures, refractory lung failure leading to death remains common. Additional therapies and treatments such as inhaled pulmonary artery vasodilators, alternative modes of ventilation such as airway pressure release ventilation (APRV), and extracorporeal membrane oxygenation (ECMO) have been utilized throughout the pandemic. Similar to their use for ARDS prior to COVID, reported outcomes have been variable but largely disappointing, certainly none emerging as the panacea for management [4,5].

High-frequency oscillatory ventilation (HFOV) offers theoretical benefit in ARDS management by emphasizing extreme lung protection from excessive volume, but essentially fell out of clinical use after 2 trials in 2013 failed to show clinical benefit, with 1 suggesting increased mortality [6,7]. Like most treatments for ARDS, evidence prior to these trials was mixed, but the negative results of these trials, combined with encouraging results from the CESAR trial investigating veno-venous ECMO [8], essentially sealed the fate of HFOV and eliminated its role in the treatment of ARDS. The impact of COVID, however, has forced the medical community to reconsider treatments from the past while searching for new treatments. With few consistently efficacious therapeutics, extreme lung protection while buying time appears paramount to good outcomes. The impact of oxygen toxicity has come to the forefront during this pandemic [9], with fibrotic lung disease often developing much quicker than observed with other pathogens. Despite mixed mortality outcomes, a large body of evidence with HFOV prior to COVID supports improved oxygenation with its use [10-12]. The benefit of lower delivered tidal volumes is unquestionable and low-tidal volume ventilation is currently the only therapeutic intervention independently associated with improved survival for patients with ARDS [13]. With this in mind, HFOV offers a potentially useful ventilation strategy for severe ARDS due to COVID-19.

Case Reports

We present 3 cases of respiratory failure due to severe COVID-19 pneumonia managed with HFOV in accordance with the CARE reporting check list. SARS-CoV-2 variants were not available to the treating team, but all 3 cases were encountered during the delta and omicron surges and were assumed to be due to one of these variants. All 3 patients were ventilated using the SensorMedics 3100B oscillator. Management of all 3 was directed by Intensivists with prior training and experience with HFOV prior to the COVID-19 pandemic. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board at Lexington Medical Center. Written informed consent was obtained retrospectively from the patients for publication of this case series and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Case 1

A 21-year-old unvaccinated, morbidly obese woman (BMI 65) was admitted 6 days after diagnosis of COVID-19. She was hypoxemic in the emergency department (ED) and required emergent intubation. She remained severely hypoxemic despite 100% FiO₂ and 22 of PEEP, so inhaled nitric oxide (iNO) was added. She was placed in prone position but continued to require 100% oxygen and high PEEP with elevated mean airway and plateau pressures in the 30s. She demonstrated evidence of sepsis, cytokine storm, and renal failure and was treated with all available therapies for COVID-19 (dexamethasone, baricitinib; no Remdesivir due to renal failure and mechanical ventilation). She remained gravely ill with no clinical improvement and required initiation of continuous renal replacement therapy (CRRT) on day 3. For refractory ARDS, she was placed on HFOV. Settings were set to allow for weaning of oxygen, and to allow for extreme permissive hypercapnia. Her FiO₂ was weaned below 60% within the first 24 hours of HFOV, and over the next 2 days her mean airway pressure (MAP) was weaned to maintain saturations of 90%. By day 3 of HFOV she had weaned to acceptable settings and her respiratory acidosis improved. She was transitioned to conventional ventilation with a high PEEP strategy. Over the next 3 days, her PEEP was weaned and neuromuscular blockade discontinued. Given her body habitus, she underwent early tracheostomy on ventilator day 8. Ventilator settings were slowly weaned, she transitioned to tracheostomy collar continuously on hospital day 17, and transferred out of the intensive care unit (ICU) on day 18. She was weaned to room air on day 23. Her renal function recovered, no longer requiring renal replacement therapy, and she discharged home on day 32.

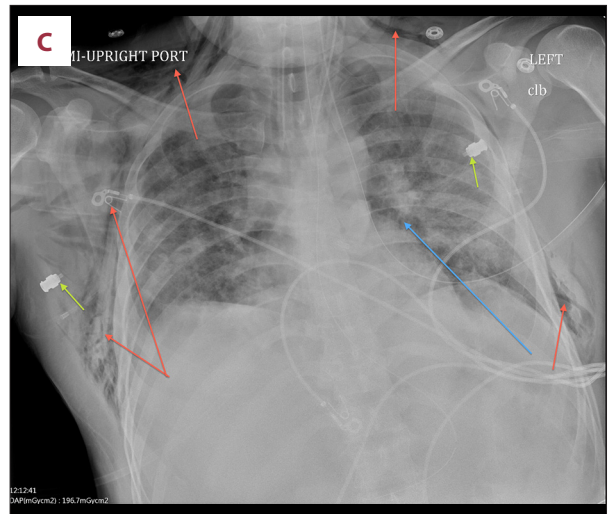
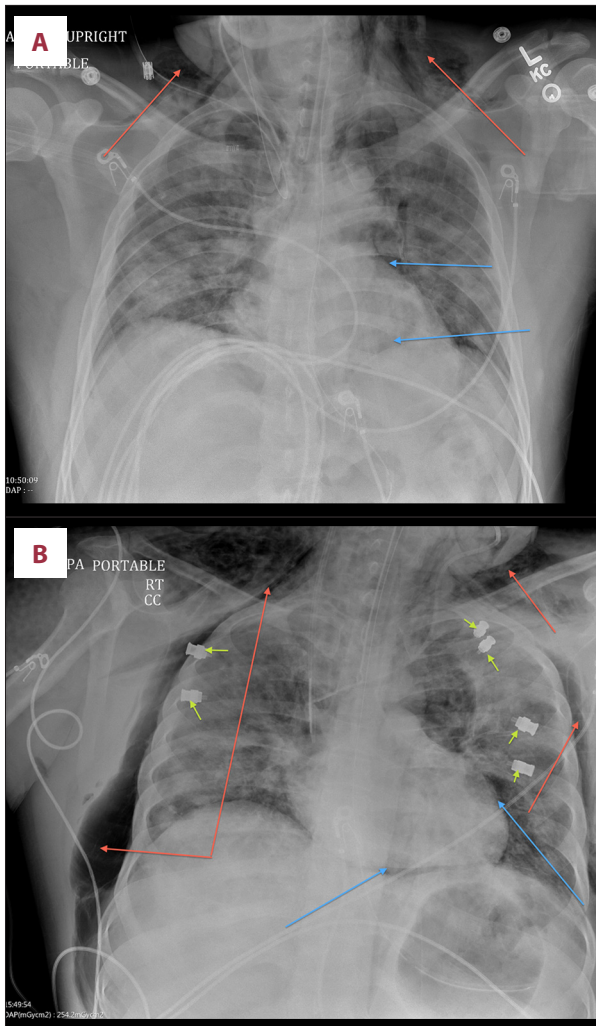


Figure 1. (A) Chest X-ray on day 3 of conventional mechanical ventilation, demonstrating the development of relatively mild subcutaneous emphysema (red arrows) and mild pneumomediastinum (blue arrows). Note these findings are present despite the absence of pneumothorax. (B) Chest X-ray on conventional ventilation, just prior to transition to HFOV, demonstrating marked worsening of subcutaneous emphysema (red arrows) and pneumomediastinum. Fenestrated subcutaneous catheters (yellow arrows) placed bilaterally for evacuation of subcutaneous emphysema. Note there is still no pneumothorax. (C) Chest X-ray on day 6 of HFOV, just prior to transition back to conventional ventilation, demonstrating markedly improved subcutaneous emphysema (red arrows) and pneumomediastinum (blue arrows). Two fenestrated subcutaneous catheters remain in place.

Case 2

A 53-year-old unvaccinated woman presented to the ED with cough, fever, and dyspnea for 1 week. A chest X-ray showed bilateral infiltrates and she was hypoxemic with positive PCR for COVID-19. She required intubation in the ED and was admitted to the ICU. COVID-19 treatments were limited due to shock with renal failure but she was started on corticosteroids and baricitinib. Initial arterial blood gas (ABG) revealed severe hypoxemia and hypercapnia, and iNO was started. Prone ventilation was attempted but she worsened clinically and required emergent supination. With refractory hypoxemia, hypercapnia, and hemodynamic instability on 100% FiO₂ and 14 of PEEP, she was placed on HFOV on hospital day 2. She remained critically ill and required vasopressor support along with CRRT for renal failure, acidosis, and volume control. Empiric antibiotics were started for possible superimposed bacterial pneumonia. Mean airway pressure was maintained and oxygen preferentially weaned, with settings again allowing for extreme permissive hypercapnia. Over the next several days, MAP was slowly

weaned and she was transitioned to conventional ventilation on hospital day 5. She was managed with a high PEEP strategy, slowly weaned, and underwent tracheostomy on hospital day 17. She was liberated from the ventilator and transferred out of the ICU on hospital day 24. Her tracheostomy tube was removed on day 34 and she was discharged to rehab on hospital day 44 on 2L nasal cannula, still requiring intermittent hemodialysis but with improving urine output, encouraging for eventual renal recovery.

Case 3

A 38-year-old unvaccinated man presented to the ED with progressive dyspnea, cough, and fevers 5 days after being diagnosed with COVID-19. A chest X-ray showed bilateral infiltrates and he was hypoxemic, requiring heated high-flow nasal cannula (HHFNC). He was admitted to the hospital ward and started on dexamethasone, Remdesivir, and baricitinib. He gradually worsened and required transfer to the ICU on hospital day 5. He was intubated on arrival, placed in prone position, and

started on iNO. He initially improved and was returned supine. On day 3 of intubation he became more hypoxemic and a chest X-ray revealed subcutaneous emphysema with pneumomediastinum (**Figure 1A**). Fenestrated subcutaneous catheters were placed but he continued to worsen with worsening hypoxemia, hypercapnia, and worsening subcutaneous emphysema/pneumomediastinum (**Figure 1B**). He was placed on HFOV, again allowing for permissive hypercapnia and in this case aggressively weaning MAP to avoid further barotrauma. He transitioned off HFOV to conventional ventilation on day 6 of HFOV with a chest X-ray showing improvement of pneumomediastinum and subcutaneous emphysema (**Figure 1C**). A low tidal volume, a low PEEP strategy was implemented, continuing to allow for hypercapnia. His neuromuscular blocker was discontinued, sedation was weaned, and he was extubated on ventilator day 12. He transferred out of the ICU on hospital day 19, weaned off oxygen, and discharged home on hospital day 28.

Discussion

The management of ARDS changed drastically with the results of the landmark ARMA trial published in 2000, which demonstrated a nearly 9% decrease in mortality utilizing a low-tidal volume strategy [13]. The standard of care became universal seemingly overnight. Prone ventilation, when combined with low tidal volume ventilation has since been demonstrated to further improve survival [2]. Nevertheless, the mortality rate remains unacceptably high, approaching 50% in some populations [14]. The search for other efficacious ventilation strategies and management has remained largely disappointing, with numerous medications and ventilator modalities proving to be largely ineffective. VV ECMO offers promising treatment, in part by limiting tidal volumes to an extreme, but is highly invasive, labor intensive, heavily consumes resources, and is often available only at tertiary medical centers. Furthermore, outcomes for COVID-19 have been inconsistent [5].

Here we present 3 patients, all previously healthy, who rapidly worsened from COVID-19 despite all available medical therapies for COVID-19 and evidence-based ventilator management. While evidence is lacking, inhaled nitric oxide was added in all 3 in an effort to improve oxygenation and limit injurious ventilator settings. With refractory hypoxemia and the availability of HFOV at our institution, our team placed each patient on HFOV.

The theoretical advantages of HFOV center around improving oxygenation through increased mean airway pressure while protecting the lungs from the high distending alveolar pressures and tidal volumes associated with increased mortality. The value of low-tidal volume ventilation was established in 2000 as the undeniable standard of care. Results have been confirmed

in many trials that have followed, and further analysis from the same trial showed that within the low tidal volume group, patients with lower plateau pressures had longer survival than those with higher plateaus [13]. Management with HFOV allows for extreme lung protection by ventilating using tidal volumes smaller than anatomic dead space, thus maximizing the only known independent lung-protective ventilation intervention.

With this strategy often comes the concept of permissive hypercapnia. The safety of this strategy has long been established, trading “normal” ABG results for the benefit of lung-protective tidal volumes. This may be of additional importance in the case of air-leak syndromes, such as patient 3, where targeted tidal volumes may be even lower than traditional goals. Excessive barotrauma has been reported with COVID-19 and is associated with increased morbidity and mortality [15]. HFOV allows for high MAP, with much of the pressures dissipating prior to reaching the distant alveoli, thus allowing for less damage and potentially quicker healing. While safe CO₂ and pH values are somewhat arbitrary, we allowed for extreme values, which we determined to be safe based on favorable hemodynamics in our patients.

Despite discouraging survival outcomes in the 2 most recent randomized trials on HFOV, most prior evidence does support improved oxygenation using HFOV, particularly when combined with inhaled nitric oxide [10-12,16]. While difficult to quantify, the potential of oxygen toxicity has come to the forefront during the pandemic, with a seemingly abnormal proportion of patients developing irreversible lung damage and fibrosis despite lack of progression to multiple organ failure, which is most often cited at the cause of death from traditional ARDS. With HFOV, our management strategy was to quickly lower FIO₂ as low as possible while maintaining mean airway pressures to safely and effectively oxygenate and ventilate. Each of our patients was able to wean quickly, within the first 24 hours of transitioning to HFOV, limiting exposure to high-dose oxygen.

Conclusions

While HFOV has fallen out of favor and should not be routinely utilized in management, we believe it should be considered in select cases when hypoxemia persists and/or standard goals cannot be accomplished. As with any therapy or intervention, it is less likely to be efficacious when used as a rescue therapy and if used, should only be used by experienced clinicians, relatively early in the clinical course of illness.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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