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Oxygen therapy strategies and techniques to treat hypoxia in COVID-19 patients

B. JIANG[1,2], H. WEI[1]

[1]Department of Anaesthesiology and Critical Care, University of Pennsylvania, Philadelphia, PA, USA
[2]Department of Anaesthesiology, Peking University People's Hospital, Beijing, China

Abstract. – OBJECTIVE: Hypoxia is one of the primary causes that leads to multiple organ injuries and death in COVID-19 patients. Aggressive oxygen therapy for the treatment of hypoxia is important in saving these patients. We have summarized the mechanisms, efficacy, and side effects of various oxygen therapy techniques and their status or the potential to treat hypoxia in COVID-19 patients. The benefit to risk ratio of each oxygen therapy technique and strategy to use them in COVID-19 patients are discussed. High flow nasal cannula oxygen (HFNO) should be considered a better choice as an early stage oxygen therapy. Supraglottic jet oxygenation and ventilation (SJOV) is a promising alternative for HFNO with potential benefits.

Key Words:
COVID-19, Oxygen therapy, High flow nasal oxygen (HFNO), High frequency jet ventilation (HFJV), Supraglottic jet oxygenation and ventilation (SJOV).

Introduction

High mortality in critically ill patients with COVID-19 is reported to reach up to 61%[1,2]. The primary pathophysiology in these patients is the progressive hypoxia due to lung damage and associated multiple organ damage[3-7]. Aggressive treatment using tracheal intubation and conventional mechanical ventilation seems not to benefit patients or even be harmful[8]. The highest mortality among those COVID-19 patients on ventilators was reported up to 86%[9]. It was suggested that COVID-19 did not cause a "typical" acute respiratory distress syndrome (ARDS)[10], so different strategies for respiratory treatments should be considered in these patients[8]. Therefore, we have summarized the mechanisms and side effects of commonly used measures or techniques for oxygen therapy in COVID-19 patients to maximize oxygen therapy benefits, minimize the risks, and hopefully, reduce mortality in COVID-19 patients.

Oxygen Nasal Cannula and Face Mask

Nasal oxygen cannula is the most commonly used initial step for oxygen therapy in patients with mild hypoxia, due to its simplicity, reduced cost, and ease of use. It is also considered to have minimal aerosol generation and a low risk of spreading the virus in COVID-19 patients. However, it can only provide up to 40% inspired fraction of oxygen (FiO2) and requires humidification when oxygen flow is above 6 litres per minute. Therefore, nasal oxygen cannula typically cannot provide efficient oxygen therapy in a patient with severe hypoxia due to significant lung damage[11]. Oxygen face masks, especially non-rebreathing face masks can provide high FiO2 oxygen therapy, but does not increase oral pharyngeal pressure, and is therefore not efficient enough to treat hypoxia due to severe lung damage and significant alveolar collapse.

High Flow Nasal Oxygenation (HFNO)

High flow nasal cannula oxygen (HFNO) therapy is used increasingly in adults with acute respiratory failure before invasive ventilation[12-14], which delivers warm, humidified oxygen through the pliable nasal cannula with a fraction of inspired oxygen (FiO2) up to 1.0 and maximum flow rate up to 70 L/min. At the beginning of the COVID-19 pandemic, due to the lack of invasive mechanical ventilators, insufficient critical care physicians, and its ease of use, HFNO have been used in some COVID-19 patients for oxygen therapy[15]. In a retrospective, multicentre cohort study from Wuhan China, HFNO was used in 21% of adult patients who were diagnosed with COVID-19[1]. In another study from Wuhan, the

Corresponding Author: Huafeng Wei, MD, Ph.D; e-mail: Huafeng.wei@pennmedicine.upenn.edu

percentage of confirmed patients in ICU who received HFNO or non-invasive ventilation (NIV) was 62%, and 7% outside the ICU[16]. In the Seattle Region, USA, 42% of the critically ill patients received HFNO[17]. A study[9] comparing the characteristics between survivors and non-survivors indicated that 85% of the survivors and 50% of the non-survivors received HFNO. Additionally, 14% of patients were treated with HFNO before intubation[3], and 34.5% of patients who died of COVID-19 received HFNO[15].

It is generally agreed that HFNO is more efficient than conventional oxygen therapy (COT) by the nasal cannula or oxygen face mask in terms of oxygenation[18]. In comparison to non-invasive ventilation (NIV), HFNO is more comfortable and easily tolerated, in addition to its simplicity for application[19]. The risks of treatment failure and 30-day mortality were not significantly different between HFNO and NIV as first-line therapy in respiratory failure[12]. The side effects associated with the use of NIV (skin breakdown) lead to the recommendation of the HFNO[19,20]. Additionally, HFNO reduces intubation rates in acute respiratory failure[13,21], while NIV may increase the intubation rate or delay the tracheal intubation[22]. In patients with non-hypercapnic acute hypoxemic respiratory failure which is frequently caused by pneumonia, one randomized control study[23] reported that the 90-day mortality rate was lower with HFNO than with NIV or COT. Similarly, a multi-centre retrospective study revealed HFNO was associated with a lower risk of 30-day mortality in patients with pneumonia or patients without hypercapnia[12]. The washout effect on the upper airway of HFNO without increasing tidal volume might be associated with less risk of aggravating lung injury due to excessive lung expansion[24]. Considering the high rate of pneumothorax in COVID-19 patients[3], HFNO may be a better choice than NIV. Besides that, HFNO was reported to improve airway clearance due to the humidified air and might be more suitable for patients with excessive secretion[25,26]. It was reported 28%-34% of patients infected with COVID-19 produced sputum and a higher proportion of 35-42% in ICU[16,17,27]. Overall, the use of HFNO is supported.

However, most protocols for airway management for patients with COVID-19 now consider HFNO a relative contraindication[28-30]. The major concern is HFNO may increase virus aerosol spreading. Aerosol transmission of SARS-CoV-2 is plausible since the virus can remain viable and infectious in aerosols for hours[31]. A recent study[32] of SARS-CoV-2 aerosolization recorded the highest airborne concentrations by personal samplers while a patient was receiving oxygen through a nasal cannula. Therefore, it is a reasonable concern that HFNO may aerosolize more viruses. Furthermore, it is reported that the distance of droplet dispersion from coughing increased by an average of 0.42 m when HFNO was used[33]. However, a randomized controlled crossover trial showed that HFNO was not associated with increased air or contact surface contamination by bacteria[34]. Also, a systematic review of aerosol-generating procedures in SARS patients suggested HFNO did not increase the risk of SARS transmission significantly[35]. Besides, it was reported that HFNO with good interface fitting was associated with a low risk of airborne transmission[36]. It should also be noted that aerosols and droplets are generated during speech[37]. Aerosols from infected persons may pose an inhalation threat even at considerable distances and in enclosed spaces, particularly if there is poor ventilation[38]. Therefore, the risk always exists even without the use of HFNO. The meaningful effort is to instruct the patients to wear surgical masks during HFNO treatment to reduce the risk of virus transmission[39,40] as long as precaution measures are taken to prevent barotrauma complications, HFNO devices are at least used in single occupancy negative pressure airborne isolation rooms with an anteroom between patient rooms and clear area. It is also highly recommended that healthcare workers should wear full airborne personal protective equipment too.

Another caution regarding HFNO, in comparison to NIV, is the association with a greater risk of treatment failure in patients with cardiogenic pulmonary edema or hypercapnia[12]. Nevertheless, the COVID-19 patients that required passive oxygen therapy experienced mainly hypoxemic respiratory failure[41]. Also, it should be noted HFNO could be applied in mild and moderate non-hypercapnia cases, but patients should be assessed for respiratory failure. It is also suggested that if there is no improvement within one or two hours, endotracheal intubation and mechanical ventilation should be considered[3,42].

Non-Invasive Ventilation (NIV)

Traditional NIV is primarily composed of continuous positive airway pressure (CPAP) or Bi-level positive airway pressure (BiPAP) ventilation[13,21,43]. NIV has been used in oxygen/ventilation therapy in SARS and H1N1 infected patients.

In recent studies[2,3], NIV was used up to 70% in COVID-19 patients before tracheal intubation for invasive mechanical ventilation. However, it seemed that the mortality in these patients was high. It has also been reported that NIV may delay the intubation in patients with severe respiratory failure and is not recommended[44-46]. NIV has also been demonstrated to increase mortality in some patients with respiratory failure. Another recent study recommends HFNO, rather than the traditional NIV, to be used for oxygen/ventilation therapy in patients with severe pulmonary failures including those caused by pneumonia[12]. While the role of traditional NIV for treatment of COVID-19 patients is still not clear, the benefit to risk ratio of NIV seems to be lower than HFNO although more studies are needed to confirm this assumption. Recent international expert recommendations[30] suggested that HFNO should be used before NIV in critically ill COVID-19 patients. If NIV is used, it should be limited to short periods with close monitoring of pulmonary failure and decision for early tracheal intubation for invasive ventilation.

Helmet Ventilation

Helmet ventilation is an alternative mode of NIV, with a helmet to replace a commonly used face mask[47-49]. Although it lacks sufficient clinical support, it is plausible to expect that the helmet has the following advantages over a face mask in COVID-19 patients: (1) reduces air leakage during positive pressure ventilation and makes the NIV more efficient; (2) the helmet helps to minimize the aerosol spreading of the SARS-CoV-2 virus; (3) patients may tolerate the helmet more than the face mask. The helmet also has the following limitation: (1) requirement of high flow of gases (more than 100 litres per minute and high consumption of oxygen supplies), with the difficulty of humidification; (2) patient's movement of head and body; (3) potential rebreathing and carbon dioxide retention, especially at low inspiratory flow. Although Helmet seemed to be widely used in COVID-19 patients in Italy, its effectiveness and side effects to treat pulmonary failure and reduce mortality are not clear at this time. No international expert recommendation could be provided[30].

Conventional Mechanical Ventilation (CMV)

Some studies[1,16] suggested that about 10-17% of COVID-19 patients eventually require trachea intubation or tracheostomy for invasive ventilation using a conventional mechanical ventilator. However, there seems to be high mortality for COVID-19 patients after tracheal intubation and CMV[9,17]. Although it is not clear, the following risk factors may contribute to high mortality after tracheal intubation: (1) patient was intubated too late and there have been multiple organ damage injuries due to severe hypoxia[3,4]. However, the consistent high mortality after tracheal intubation during this pandemic around the world has inspired alternative techniques, such as HFNO, for oxygen/ventilation treatment in COVID-19 patients and avoiding CMV, although there is no clear conclusion at this moment; (2) the complications, such as pneumothorax, etc. associated with high-pressure ventilation during CMV worsen the lung damage[3]; (3) the COVID-19 patients on CMV usually had multiple organ injuries, a risk factor for COVID-19 patient mortality[50].

High Frequency Jet Ventilation (HFJV)

High frequency jet ventilation (HFJV) is characterized by its open system, high frequency (Respiratory rate >60/minutes), small tidal volume, and low airway pressures[51]. The open system makes it convenient during airway surgery, such as rigid scope vocal cord examination or surgery and airway management, such as transtracheal jet ventilation (TTJV) for elective or emergent difficult airway management. High frequency can minimize the diaphragm movement and therefore benefit the atrial fibrillation (AF) ablation. Low airway pressure and low tidal volume may benefit the oxygen/ventilation in ARDS treatment or during hypovolemic shock. HFJV at a frequency close to heart rate or synchronized with heart rate also assists cardiovascular function[52,53].

Previous studies[52,54-56] suggested that high frequency jet ventilation (HFJV) may provide better oxygenation than CMV in the treatment of respiratory failure or ARDS caused by various reasons, including pneumonia, surgery, trauma etc. Although these reports did not indicate that HFJV is better than CMV in reducing mortality in the treatment of severe pulmonary failure or ARDS, they provided alternative mechanical ventilation with similar efficacy for these treatments. With its limitation of difficulty to monitor FiO2, airway pressure, PetCO2 due to its open system, and the difficulty of humidification of the inhaled gases, it is not widely used now for the treatment of pulmonary failure or ARDS. With its characteristics of better oxygenation

under the condition of small tidal volume and low airway pressure, HFJV is expected to treat hypoxia in COVID-19 patients efficiently, especially for those with severe pulmonary failure or ARDS.

High Frequency Two-Way Jet Ventilation (HFTJV)

High frequency two-way jet ventilation is composed of both active inspiratory and expiratory phases. During the inspiratory phase, a jet pulse is injected into the lung, while a jet pulse is injected out of the lung during the expiratory phase[57,58]. Compared to regular HFJV, the active exhalation by the reverse jet pulse during the expiratory phase, not only further decreases mean airway pressures (approach to 0) but also enhances oxygenation/ventilation and improvement of circulatory function[57]. Considering the importance of treating hypoxia and often associated circulatory dysfunctions in ARDS patients, HFTJV theoretically provides the greater capability of improving cardiopulmonary functions than CMV or regular HFJV. Additionally, the reverse jet pulse inside the trachea generates active expiration and may eliminate the SARS-CoV-2 virus out of the lungs due to the Venturi effects generated by the reverse jet pulses. We predict that HFTJV can reduce mortality in COVID-19 patients, compared to traditional CMV. Therefore, it is important and urgent to investigate the effectiveness and side effects of HFTJV in the treatment of COVID-19 patients with ARDS.

Supraglottic Jet Oxygenation and Ventilation (SJOV)

HFJV is typically performed as the infraglottic jet ventilation, with jet pulses originated below the vocal cord. This usually requires tracheal intubation and placement of the endotracheal tube and therefore deep sedation for patients to tolerate it. Many studies[59-64] suggested that supraglottic jet oxygenation and ventilation (SJOV) with jet pulses originated above the vocal cords, can also maintain similar efficacy of oxygenation/ventilation as HFJV, as long as the jet pulses are directed towards vocal cord. Compared to the regular infraglottic HFJV, SJOV has the following characteristics: (1) easy, quick, and convenient to set up and use; (2) easy to learn and train, even patients can do it themselves through synchronizing their inhalation with the inspiratory jet pulses (YouTube video: https://youtu.be/DXhfEMX5o6U); (3) monitoring of breathing function with the ability to monitor PetCO2; (4) minimizing the barotrauma complications frequency seen in the transtracheal jet ventilation (up to 30% in emergent airway management)[65], due to its guarantee of opening systems by opened mouth and nose during SJOV. Several scholars[60,62,66] have demonstrated that SJOV could be effective in maintaining adequate oxygenation/ventilation in patients with respiratory suppression due to propofol infusion or general anesthesia, and in apnea patients because of muscle relaxants administration[59,62]. SJOV has been used in patients receiving gastrointestinal endoscopy under propofol infusion, elective and emergent difficult airway management, and especially in obese patients with obstructive sleep apnea (OSA)[61,62,67,68].

HFNO has been increasingly used to treat hypoxia in COVID-19 patients as described above. Compared to HFNO, SJOV not only provides similar efficacy of oxygenation even in apnea patients but also ventilation and maintenance of blood carbon dioxide levels[64]. Hence, SJOV is expected to treat hypoxia in COVID-19 patients, especially during the early phase of the disease. SJOV may have the following advantages in the treatment of hypoxia in COVID-19 patients: (1) it is easy to use and relatively tolerable in non-sedated patients, which makes its use applicable for the treatment of hypoxia at early stages. This is especially true when the WNJ is placed in the mouth to generate SJOV with the injection of jet pulses synchronized with patients' inhalation controlled by patients themselves (YouTube video: https://youtu.be/DXhfEMX5o6U); (2) it can be easily adjusted from treating mild hypoxia to moderate or severe hypoxia by increasing driving pressures and change of position of WNJ from mouth to nose under mild sedation[60]; (3) it requires less sedation than NIV but provides efficient oxygenation/ventilation and may be used to avoid tracheal intubation; (4) it may provide similar efficacy on oxygenation and ventilation, but reduced use of sedation requirement compared to the conventional mechanical ventilation.

Similar to HFNO, SJOV is a ventilation technique that has the potential to generate aerosol transmission of the SARS-CoV-2 virus. If SJOV is used to treat hypoxia/hypercapnia in COVID-19 patients, it should be performed in a negative pressure room with an anteroom between patients' rooms and clean area. Adequate PPE should be worn to protect health care workers from cross-infection.

Conclusions

In summary, aggressive oxygen therapy to correct hypoxia is critical for the successful treatment of COVID-19 patients and the reduction of mortality. Nevertheless, the effectiveness of conventional mechanical ventilation as the main treatment modality has been queried due to the non-uniformity of COVID-19 compared to the conventional pulmonary failure and ARDS[8,10]. We summarized the benefit/risks ratio of various oxygen therapy techniques and hope this will help to establish adequate treatment and improve the outcome in COVID-19 patients. Generally, before the late stage, during which overt edema and shunt have developed and only invasive mechanical ventilation could work, HFNO should be considered a better choice as an early stage oxygen therapy. SJOV is a promising alternative for HFNO with potential benefits, though further studies are still needed. As an alternative for invasive conventional ventilation, HFJV or HFTJV might be considered.

Conflict of Interest

The Authors declare that they have no conflict of interests. Huafeng Wei is the inventor of WEI Nasal Jet Tube (WEI NASAL JET, WNJ) to perform supraglottic jet oxygenation and ventilation (SJOV), and a consultant of Well Lead Medical Company, Guangzhou, China. Well Lead Medical Company has licensed WNJ from the University of Pennsylvania Trustee.

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Authors' Contribution

All authors contributed to the conception and writing of this manuscript.

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