EDITORIAL

Alternatives to Invasive Ventilation in the COVID-19 Pandemic

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Since its invention in the 1940s, the positive pressure ventilator has always been known to have both risks and benefits. Although mechanical ventilation is unquestionably lifesaving, there are numerous associated drawbacks. Beyond the obvious and immediate limitations that patients require translaryngeal intubation and are physically attached to a ventilator, delivery of gas by positive pressure also creates mechanical stress and causes strain on lung tissue. This stress can lead to ventilator-induced lung injury, compounding the underlying lung condition that precipitated the initial respiratory failure.[1] Despite advances in knowledge about protective ventilation strategies to limit ventilator-induced lung injury (most notably use of low tidal volumes), concern remains for this iatrogenic injury in all patients undergoing intubation and mechanical ventilation.

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While noninvasive ventilation (NIV) techniques (ie, techniques that avoid translaryngeal intubation) have substantially reduced the need for invasive mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease and cardiogenic pulmonary edema, defining the role of these techniques in acute hypoxemic respiratory failure (AHRF) from lung injury has remained elusive. Initial reports of improved outcomes with NIV delivered by face mask in immunocompromised patients[2,3] were later questioned in a larger clinical trial.[4] Although high-flow nasal cannula (HFNC), another method of noninvasively delivering oxygen, seemed poised to fill an important gap for this vulnerable population, a clinical trial involving more than 700 patients found that HFNC did not significantly improve survival.[5] As the pursuit to spare patients exposure to invasive ventilation in AHRF continues, there is a countermovement questioning the wisdom of such an approach, given concerns that spontaneous breathing at large tidal volumes during use of NIV or HFNC may exacerbate lung injury.[6]

Coronavirus disease 2019 (COVID-19), which causes one type of AHRF, has accelerated the need to add clarity to this ongoing debate of whether to intubate early and, if not, which type of noninvasive support (NIV, HFNC, or standard oxygen therapy) is the most efficacious. Early series suggested high mortality for patients with COVID-19–associated respiratory failure who received invasive mechanical ventilatory support,[7] raising the concern that these patients may be particularly vulnerable to ventilator-induced lung injury. In addition, the surge of patients in some locales has already strained and exceeded the capacity of some health care facilities, including availability of ventilators. Strategies that could at least safely spare patients invasive ventilation or shorten the duration of invasive ventilation could be of enormous importance. Thus, a useful assessment of the existing literature informing such decisions would be welcome.

In this issue of *JAMA*, Ferreyro et al[8] report findings from a network meta-analysis that evaluated the association of noninvasive oxygenation strategies (with comparisons among face mask NIV, helmet NIV, HFNC, and standard oxygen therapy) with outcomes in adults with AHRF. The use of a network approach leverages direct evidence from published clinical trials that share common comparators to generate indirect evidence to rank order them. For example, given that no clinical trial has compared helmet NIV with HFNC, separate clinical trials that directly compared helmet NIV[9] and HFNC[10] with a common comparator, face mask NIV, could be used to generate indirect evidence for the relative benefit associated with helmet NIV vs HFNC.

The authors included 25 studies with 3804 patients with AHRF in this analysis and found that compared with standard oxygen therapy, helmet NIV (based on 3 trials with 330 patients; network risk ratio [RR], 0.26; 95% credible interval [CrI], 0.14-0.46), face mask NIV (14 trials with 1725 patients; RR, 0.76; 95% CrI, 0.62-0.90), and HFNC (5 trials with 1479 patients; RR, 0.76; 95% CrI, 0.55-0.99) were associated with a lower risk of endotracheal intubation. Both forms of NIV, helmet (RR, 0.40; 95% CrI, 0.24-0.63) and face mask (RR, 0.83; 95% CrI, 0.68-0.99), were also associated with a lower risk of death.

Even though these overall findings suggest the potential benefits of noninvasive oxygenation support, there are nuances to these data, which are revealed in the various sensitivity analyses. The association of face mask NIV with lower mortality was no longer statistically significant among patients with severe hypoxemia (Pao_2:Fio_2 ratio ≤200) after excluding trials that included patients known to have established benefit from NIV, specifically those with chronic obstructive pulmonary disease, heart failure, and postoperative state. Furthermore, the association of face mask NIV with rates of endotracheal intubation was also not statistically significant when noninformative priors were considered to account for the views of clinicians who may have greater confidence in HFNC than in face mask NIV. These analyses illuminate the controversial role of face mask NIV in the management of severe AHRF, as prior studies[10,11] have suggested increased harm, possibly due to excessive tidal volumes, high transpulmonary pressures, and resulting patient self-inflicted lung injury.[6] However, these sensitivity analyses did not alter the association of helmet NIV with reduced rate of intubation and reduced mortality, suggesting that any evaluation of the potential role in AHRF should incorporate the interface by which NIV is applied.

The physiologic effects of helmet and face mask NIV may differ in AHRF. With face mask NIV, pressure support is often needed to reduce effort,[12] potentially setting the stage for excessive and thus injurious tidal volumes. In contrast, helmet NIV is able to deliver higher levels of positive end-expiratory pressure (PEEP) to improve oxygenation, reduce inspiratory effort,[13] and possibly render spontaneous breathing noninjurious.[14] However, the certainty of the evidence supporting helmet NIV compared with all other modes of noninvasive oxygen support is low due to the limited number of available published clinical trials and small number of participants.

Questions remain for clinicians regarding when and for which patients these various noninvasive oxygen support strategies fit into the algorithm of AHRF management and specifically for patients with COVID-19. Although some have argued that the risk of spontaneous breathing should preclude any noninvasive oxygen support, the data from the analysis by Ferreyro et al indicate that it is a reasonable approach to spare a subset of patients with AHRF invasive mechanical ventilation and its inherent complications. Although this network metanalysis may suggest a rank order of potential efficacy associated with these techniques, it is clear that a one-size-fits-all approach to AHRF is misguided. Choosing the right noninvasive oxygen support likely requires a precision-based approach that matches a given strategy to the observed phenotype of AHRF coupled with incorporating clinician experience and comfort with each technology. For instance, perhaps lung injury that is nonresponsive to PEEP is best served with a trial of HFNC. Alternatively, NIV may be considered if the lung injury seems PEEP responsive, with milder hypoxemia (Pa_{O_2}:F_{IO_2} ratio >200) reserved for the face mask interface and severe hypoxemia with a prolonged need of NIV application reserved for helmet.

Although further studies are needed, the meta-analysis by Ferreyro et al has provided a useful summary of the available data to help inform clinicians as they determine locally the best way to choose wisely among several options for care of patients with AHRF, especially in the wave of patients with COVID-19 currently being encountered. Future clinical trials comparing these strategies should not focus on declaring a "winner" per se but rather on identifying the patient phenotypes that stand to benefit from each noninvasive oxygenation support method. In the management of heterogeneous syndromes like AHRF, it is better to have multiple options than to focus on limiting clinical practice to a single choice.

ARTICLE INFORMATION

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Published Online: June 4, 2020. doi:10.1001/jama.2020.9611

Conflict of Interest Disclosures: Dr Patel reported receipt of grants from the Parker B. Francis Foundation outside the submitted work. No other disclosures were reported.

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