EDITORIAL

# Defining Optimal Respiratory Support for Patients With COVID-19

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**Noninvasive respiratory support** is an essential component of critical care. Both noninvasive ventilation, with its different interface types and modes (including helmet and face masks), and high-flow nasal oxygen (HFNO) are successfully used to manage patients with acute hypoxemic respiratory failure. Noninvasive respiratory support can alleviate respiratory distress, improve oxygenation, and possibly reduce the need for invasive mechanical ventilation.[1,2] Due to known adverse effects associated with invasive mechanical ventilation (eg, sedation, ventilator-induced lung injury, predisposition for infections), it is conceivable that noninvasive respiratory support may reduce mortality through reduction in the need for tracheal intubation.[3,4] However, noninvasive ventilation may inappropriately delay tracheal intubation and increase patient self-inflicted lung injury, which may occur at varying degrees depending on the type and interface of noninvasive ventilatory support.[5,6] The intense respiratory efforts by patients who are spontaneously breathing contribute to and exacerbate acute lung injury.

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Due to the complexity in the causes and presentations of acute respiratory failure, several randomized clinical trials are needed to clarify the specific roles of noninvasive respiratory support. However, the evaluation of respiratory support strategies for acute illness is challenging for several reasons. First, it is difficult to achieve a balance among trial protocol executability, comprehensiveness, and completeness. Second, the concomitant evaluation of pharmacological treatments[7,8] for acute illnesses like COVID-19 are often initiated without considering the variability and evidence for nonpharmacological therapies like noninvasive respiratory support. Third, debate outside the context of randomized clinical trials may undermine the perception of equipoise for some respiratory interventions.[9,10]

In this issue of *JAMA*, Perkins et al[11] report the Randomized Evaluation of COVID-19 Therapy-Respiratory Support (RECOVERY-RS) platform trial that assessed whether noninvasive ventilation (in the form of continuous positive airway pressure [CPAP] without the use of additional inspiratory pressure) or HFNO was more effective than conventional oxygen therapy for hospitalized patients with COVID-19. The large pragmatic trial included patients with hypoxemia (oxygen saturation as measured by pulse oximetry of ≤94%) despite receiving oxygen (fraction of inspired oxygen ≥0.40). The trial functioned as 2 trials that shared a single control group (CPAP vs conventional oxygen therapy and HFNO vs conventional oxygen therapy). Randomization was performed on the basis that the therapies were available at the enrollment site, acknowledging specific contraindications for each type of noninvasive respiratory support, and using a minimization algorithm for trial group imbalances. The primary outcome was a composite of tracheal intubation or mortality within 30 days. The trial was stopped early in May 2021 due to a reduction in the number of COVID-19 cases and the termination of funding. Therefore, although all precautions had been made by the authors to ensure a fair reporting and analysis, trial interruption before reaching the expected sample size may have unpredictable consequences on the effect size estimates and the analysis of the secondary outcomes.

After enrolling 1273 participants (380 randomized to CPAP, 418 to HFNO, and 475 to conventional oxygen therapy), the reported frequency of the primary outcome was 36.3% for CPAP vs 44.4% for conventional oxygen therapy (absolute difference, −8% [95% CI, −15% to −1%]), suggesting that the results were compatible with reductions as large as 15% and as low as 1%. The reported frequency of the primary outcome was 44.3% for HFNO vs 45.1% for conventional oxygen therapy (absolute difference, −1% [95% CI, −8% to 6%]), suggesting that the results were compatible with reductions as large as 8% and increases as large as 6%. The reduction in the primary outcome for the comparison between CPAP and conventional oxygen therapy was mostly driven by a reduction in the need for invasive mechanical ventilation (33.4% vs 41.3%, respectively) and not by differences in mortality (16.7% vs 19.2%). An inverse probability weighting analysis that accounted for crossovers to the other treatment groups resulted in similar estimates. In a post hoc analysis that compared CPAP vs HFNO, CPAP was associated with an absolute reduction of 10% for the primary outcome (the wide compatibility margins for the absolute difference ranged from a remarkable 18% reduction to a smaller but still clinically relevant 2% reduction). Adverse events were reported in 34.2% of participants in the CPAP group, 20.6% in the HFNO group, and 13.9% in the conventional oxygen therapy group.

A key finding from this trial, albeit somewhat unsettling, was that noninvasive ventilation reduced tracheal intubation but not mortality. Reducing the need for tracheal intubation is clinically relevant, and especially important during a pandemic with staff and equipment shortages. However, the interpretation of a reduction in tracheal intubation without a reduction in mortality can be challenging. This is a common situation when a composite primary outcome of sequential events is used in a clinical trial. Assuming that most patients who died received invasive mechanical ventilation, a possible conclusion may be that if an intervention reduced the need for tracheal intubation but did not reduce mortality,

it most likely reduced the need for tracheal intubation among patients with less severe illness, who would eventually survive had they received invasive mechanical ventilation.

There are other potential explanations. A more nuanced interpretation relies on possible heterogeneity in the treatment effect. For example, the net benefit of CPAP may be the result of a combination of several effects among subpopulations, including: (1) a reduction in tracheal intubation among patients with less severe illness who would survive if they received ventilation; (2) an increase in the risk of death in very severely ill patients, by delaying tracheal intubation, leading to invasive mechanical ventilation followed by death; and (3) a mortality reduction for patients who received CPAP and eventually received ventilation. The second pathway, for example, could be caused by an increase in patient self-inflicted lung injury, delayed tracheal intubation with noninvasive ventilation, or both, although other combinations also are possible.

The results of the RECOVERY-RS trial[11] should be interpreted in the context of findings from other recent trials[12,13] that assessed respiratory support in patients with COVID-19. In the Helmet Noninvasive Ventilation Versus High-Flow Oxygen Therapy in Acute Hypoxemic Respiratory Failure (HENIVOT) trial,[12] patients (n = 109) with moderate or severe COVID-19 were randomized to receive noninvasive ventilation through a helmet device or HFNO. The trial yielded neutral results for its primary outcome (days alive and free of respiratory support) and for mortality; however, patients in the helmet group had a lower need for invasive mechanical ventilation. Overall, the results from the HENIVOT trial[12] are compatible with the post hoc comparison of CPAP vs HFNO in the RECOVERY-RS trial.[11]

The RECOVERY-RS trial[11] results differ from the findings of the High-Flow Nasal Cannula in Severe COVID-19 With Acute Hypoxemic Respiratory Failure (HiFLo-Covid) trial.[13] In that trial of 220 patients with COVID-19,[13] the use of HFNO reduced the rate of tracheal intubation compared with conventional oxygen therapy (34% vs 51%, respectively). Several potential reasons could be hypothesized for the differences between the results from the RECOVERY-RS trial[11] and the HiFLo-Covid trial.[13] Some possible explanations may be related to (1) different inclusion criteria (eg, the HiFLo-Covid trial[13] randomized patients with newly diagnosed [≤6 hours] acute respiratory failure); (2) differences in the severity of illness of the included patients (the HiFLo-Covid trial required signs of poor oxygenation and respiratory distress); (3) differences in trial procedures (the HiFLo-Covid trial protocolized escalation to tracheal intubation, which may have reduced the variability of physician's attitudes in a clinical scenario); and (4) differences in oxygen flow rates (60 L/min in the HiFLo-Covid trial vs approximately 50 L/min in the RECOVERY-RS trial[11]). In addition, the HiFLo-Covid trial[13] enrolled fewer patients than the RECOVERY-RS trial,[11] which may increase the chance of both signal and magnification errors.[14]

Taken together, the findings from the RECOVERY-RS trial[11] in this issue of *JAMA*, along with other recent trials,[12,13] contribute to the evidence for this challenging clinical issue. However, several questions remain. For instance, some trials used a hybrid approach when evaluating HFNO and noninvasive ventilation,[4,12] whereas others tested different methods (eg, pure HFNO, pure noninvasive ventilation with 2 pressure levels, pure CPAP, hybrid CPAP/HFNO). Thus, the evidence for some comparisons may be lacking. For example, is a hybrid approach of noninvasive ventilation combined with HFNO more effective than either method separately? Indirect comparisons that were not specifically tested in a single randomized clinical trial might be resolved through a network meta-analysis of available trials, ideally using individual patient data. In addition, the optimal delivery of noninvasive ventilation and HFNO is unknown. For noninvasive ventilation, what level of pressure is optimal, and is CPAP more effective than not adding support pressure? For HFNO, what is the optimal strategy for determining the ideal flow rate and weaning schedule as patients convalesce? The results of the ongoing High-Flow Nasal Oxygen Cannula Compared to Non-Invasive Ventilation in Adult Patients With Acute Respiratory Failure (RENOVATE) trial (NCT03643939), which compares HFNO with noninvasive ventilation in a heterogeneous population of patients with acute respiratory failure, including COVID-19, will contribute to this evidence base.

Based on the available evidence, it is reasonable to assume that noninvasive ventilation is probably beneficial to reduce the need for invasive mechanical ventilation in patients with COVID-19 who have acute respiratory failure, whereas the precise role of HFNO in patients with COVID-19 is far less clear. For the immediate future, CPAP may be recommended as a first-line therapy with combination HFNO and other hybrid approaches being considered tailored to the patient's condition and tolerance.

ARTICLE INFORMATION

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**Published Online:** January 24, 2022. doi:10.1001/jama.2022.0067

**Conflict of Interest Disclosures:** Dr Zampieri reported receiving grants from Ionis Pharmaceuticals, the Brazilian Ministry of Health, and Bactiguard. Dr Ferreira reported receiving personal fees from Medtronic.

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