High-Flow Nasal Cannula and Outcomes in COVID-19: Reading Between the Lines

Ashish K. Khanna, MD, MS, FCCP, FCCM, FASA,*†‡ Audrey De Jong, MD, PhD,§‖ and Sheila Nainan Myatra, MD, FCCM¶

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GLOSSARY

AHRF = acute hypoxic respiratory failure; **ARDS** = acute respiratory distress syndrome; **CI** = confidence interval; **COPD** = chronic obstructive pulmonary disease; **COT** = conventional oxygen therapy; **COVID-19** = coronavirus disease 2019; **HFNO** = high-flow nasal oxygen; **HR** = hazard ratio; **SILI** = self-inflicted lung injury

Noninvasive respiratory support is usually considered first-line therapy for acute hypoxic respiratory failure (AHRF). High-flow nasal oxygen (HFNO) is one approach for delivering noninvasive support and acts by delivering oxygen-enriched gas at flow rates considerably higher than standard nasal cannula or facemask strategies. HFNO increases the inspired fraction of oxygen without generating higher airway pressures, promotes CO_2 washout, and reduces respiratory rate.[1,2] HFNO is often more comfortable than mask-based noninvasive support, and in a 2015 multicenter trial comparing HFNC, noninvasive positive pressure ventilation and conventional oxygen therapy (COT) increased ventilator-free days at 28 days and 90-day mortality.[3] A meta-analysis of oxygenation with HFNC compared with COT and noninvasive ventilation for acute respiratory distress syndrome (ARDS) found lower intubation rates when HFNC was used.[4]

From the *Department of Anesthesiology, Section on Critical Care Medicine, Wake Forest University School of Medicine, Wake Forest Baptist Medical Center, Winston-Salem, North Carolina; †Perioperative Outcomes and Informatics Collaborative, Winston-Salem, North Carolina; ‡Outcomes Research Consortium, Cleveland, Ohio; §Anesthesia and Critical Care Department, Saint Eloi Teaching Hospital, University Montpellier 1, Cedex 5, France; ‖Phymed Exp INSERM U1046, CNRS UMR 9214, Montpellier, France; and ¶Department of Anesthesiology, Critical Care and Pain, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai, India.

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Address correspondence to Ashish K. Khanna, MD, MS, FCCP, FCCM, FASA, Department of Anesthesiology, Section on Critical Care Medicine, Wake Forest University School of Medicine, Perioperative Outcomes, and Informatics Collaborative (POIC), Atrium Health Wake Forest Baptist Medical Center, 1 Medical Center Boulevard, Winston-Salem, NC 27157. Address e-mail to akhanna@wakehealth.edu.

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In patients with hypoxic respiratory failure due to coronavirus disease 2019 (COVID-19), an important unanswered question is the choice of optimal type of respiratory support. Unlike patients with traditional ARDS, in whom gas-exchange deterioration is accompanied by worsening respiratory compliance, patients with COVID-19 have both hyperperfused (low V′/Q′) and hypoperfused (high V′/Q′, dead space) ground glass regions within their pulmonary parenchyma. Such patients may, therefore, be hypoxemic due to V′/Q′ mismatch and paradoxically have normal or increased static compliance.[5]

In principle, patients with hypoxemia and normal lung compliance are ideal candidates for HFNC support as they mostly require only enriched oxygen support. Once it became clear that caring for COVID-19 patients on HFNC did not result in widespread transmission of infection for caregivers, many centers transitioned to use of HFNC as first-line therapy for COVID pneumonia, with intubation only for patients who clearly failed HFNC treatment. However, the effect of this strategy on long-term outcomes in patients with COVID pneumonia remains unclear. Although noninvasive respiratory support may reduce the need for intubation, prolonged high respiratory rates and increased minute ventilation in patients receiving noninvasive respiratory support raise the possibility of self-inflicted lung injury due to high shear forces.[6,7] Whether intubating patients to prevent these self-inflicted shear forces improves overall outcomes is up for further investigation.

In this month's issue of *Anesthesia & Analgesia*, Nurok et al[8] attempt to shed some light on this dilemma. Using single-center electronic health record data, Nurok et al reviewed patients with COVID-19 who required intubation and compared the likelihood

of successful extubation and mortality with or without preexisting use of HFNO. In a cohort of 440 patients (311 of whom received HFNO), they found that patients who received HFNO before intubation had no difference in the likelihood of successful extubation, and a higher risk of in-hospital mortality (HR): 2.08; 95% confidence interval (CI), 1.06–4.05 when compared to those who were intubated without prior use of the HFNO. Survival models were adjusted for potential confounders including severity of illness. We congratulate the authors, for addressing a very important scientific question, an attempt to make best use of available data, and an elegant analysis to support the results.

At first glance, these findings suggest that the use of HFNO in COVID-19 patients before invasive mechanical ventilation may worsen mortality and decrease the likelihood of a successful outcome after intubation. However, this retrospective analysis only included patients who were intubated. The authors did not examine outcomes of patients who received HFNO (or not) and did not require intubation. This aspect of the data would have provided a more complete perspective on the usefulness (or lack of) of HFNO in COVID-19 pneumonia. Here, a finding that HFNO use worsened outcomes even in patients who did not require intubation would support the idea that self-inflicted lung injury (SILI) is clinically relevant and implies that earlier intubation may be needed in patients with COVID respiratory failure. Conversely, a finding of no difference would suggest that other factors may play a role in the association observed by Nurok et al.

Better understanding the relationship between HFNO use and outcome in COVID patients is particularly relevant as existing literature finds that HFNO use can stave off intubation in many patients with COVID-19 pneumonia.[9] A 2020 retrospective single-center study found that early application of HFNO as first-line ventilatory support during COVID-19-related AHRF obviated the need for intubation in up to a third of cases.[10] A recent systematic review also suggested that a high-flow nasal cannula may reduce the need for invasive ventilation and escalation of therapy compared with conventional oxygen therapy in patients with COVID-19 with AHRF.[11] We should note that considerable variability exists in the failure rate of noninvasive respiratory support in patients with COVID-19 and that difficulty predicting which patients will go on to require intubation also complicates the decision to intubate versus remain on HFNO.[12]

The all-important argument for association versus causality becomes even more relevant when we examine this study by Nurok et al. While the authors do a commendable job adjusting for many known covariates, residual (hidden) confounding factors may still have played a role. For example, parameters about the condition of the patient before intubation in those who received HFNO may not have been available to the authors in sufficient detail to allow the reader to understand how clinicians made the decision to intubate (or not). Examples of such variables that may have helped would be among others, subjective patient symptoms, the duration of daily support on HFNO and whether this support was cycled from maximal HFNO to minimal, use of other noninvasive modalities such as CPAP, or the trend in HFNO settings over time. In the case of COVID, intubation may have been performed to reduce health care worker infection rather than for patient failure, further complicating any association between HFNO use and outcome. Evolving treatment pathways for COVID may also have affected the study results. Nurok et al also did not clearly describe the indication for intubation in their dataset. In this study, the median duration of HFNO use before intubation was 1.6 days. Centers that intubated earlier (or later) may not have had similar results. In actuality, the trigger to intubate varied a lot even within a single institution and ICU care team, which introduces an element of heterogeneity in this analysis that may be difficult to fully overcome. Mechanical stress on the lung due to patient respiratory effort (patient SILI), which was considerable in COVID patients, may have played a role and caused harm in patients receiving HFNO.[6,7]

The question Nurok et al address is both academically and clinically relevant. Early in the COVID-19 pandemic, timeline clinicians started with "early" intubation when patients failed conventional oxygen therapy, but quickly pivoted to a "delayed" approach when clinicians recognized that many patients could be maintained on HFNO recover without intubation. Poor outcomes in patients who failed HFNC, however, have caused the pendulum to swing back somewhat. Since then, the question of optimal timing for intubation in COVID patients has remained unanswered and considerable variability in practices exists. The work of Nurok et al suggests that delaying intubation may come at a cost in patients supported with HFNO. A 2-arm interventional trial with intubation following a protocolized escalation of HFNC or continuation of HFNO escalation seems attractive. However, for obvious reasons, this type of randomized trial of early versus late intubation would be ethically difficult. As a result, retrospective associations of the type observed by Nurok et al provide the only guidance to clinical care with respect to this question.

Nurok et al[8] also provide a robust statistical analysis to strengthen the value of their results. Multivariable Cox proportional hazards models

were used to examine differences in rates of successful extubation and in-hospital mortality in patients receiving HFNO before intubation and in those not receiving HFNO. These analyses were adjusted for age, sex, race/ethnicity, Hco_3, CO_2, Spo_2:Fio_2 (S:F) ratio, vitals at time of initiation of advanced respiratory therapy, length of stay before initiation of advanced respiratory therapy, obesity, hypertension, diabetes, and chronic obstructive pulmonary disease (COPD) or asthma. To further evaluate the degree of unmeasured confounding, Nurok et al[8] calculated expectation value (E-value) for reported associations.[13] An E value estimates the magnitude of association between an unmeasured confounder and treatment, or outcome needed to explain the observed association. A higher E value, therefore, means that considerable unmeasured confounding would be needed to explain away an effect estimate. This study reports a value of 2.7, which suggests that any unmeasured confounder would need only to be moderately associated with HFNO use or hospital mortality to nullify the relationship between HFNO use and outcome observed by Nurok et al.

Although Nurok et al raise intriguing questions about the wisdom of delaying intubation in COVID patients on noninvasive respiratory support, a more cautious interpretation might be that clinicians caring for COVID patients on HFNO monitor patients closely to optimize the outcomes of intubation in COVID-19. In addition to "classic" indicators such as rising pco_2 or falling po_2, worsening respiratory distress, patient fatigue, hypotension, or worsening kidney injury, Nurok et al raise the intriguing question of whether clinicians should also consider duration and possibly amount of HFNO support. Further work on this important question is clearly needed to clarify the best approach. While we emerge from the pandemic, the lessons learned with this work may be used to construct a future appropriately designed interventional trial for non-COVID respiratory failure, though the process will be challenging.

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