Noninvasive Ventilation Strategies in the Age of COVID-19: An Evolving Story

Over the past decade, use of noninvasive oxygenation strategies (NIOS) for the treatment of hypoxemic respiratory failure, consisting mainly of noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC), has increased substantially despite a lack of supporting evidence.[1] In contrast, on the basis of studies demonstrating reduced need for intubation and mortality compared to conventional oxygen therapy, guidelines dating back > 15 y have recommended the use of NIV as first-line therapy to treat acute respiratory failure due to COPD exacerbations and acute cardiogenic pulmonary edema.[2] As recently as 2017, on the other hand, the European Respiratory and American Thoracic Society (ERS/ATS) Guideline on NIV to treat "de novo" hypoxemic respiratory failure made no recommendation, advocating neither for nor against its use, because of the weakness of the evidence.[3] In fact, the LUNG SAFE observational study on ARDS indicated that subjects with $P_{aO_2}/F_{IO_2} \leq 150$ who were placed on NIV initially had higher mortality rates (hazard ratio 1.45) than subjects intubated initially, suggesting possibly greater harm for NIV in patients with severe ARDS.[4] Then again, the study by Patel et al,[5] which showed a dramatic reduction in intubations and 90-d mortality in subjects managed with NIV administered via helmet compared to full face mask (18% vs 64% and 34% vs 56%, respectively), suggests that perhaps the problem is not NIV per se but the interface by which it is delivered.

HFNC has seen an explosion of use over the past decade, mainly for hypoxemic respiratory failure, and, once again, the supporting data are sparse. The oft-cited FLORALI study[6] randomized 313 subjects with hypoxemic respiratory failure, mainly due to ARDS or pneumonia, to either HFNC, standard oxygen therapy, or NIV and reported a significant reduction in intubations (the main outcome variable) with HFNC only in the subgroup of subjects with $P_{aO_2}/F_{IO_2} \leq 200$ (35% vs 47% vs 50%, respectively, $P < .05$). However, ICU and 90-d mortality were also significantly reduced (30% vs 45% vs 49%, respectively, $P < .05$). A subsequent meta-analysis consisting of 18 studies, including the FLORALI study, also suggested that HFNC reduced intubation rates compared to standard oxygen, but

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the authors could not substantiate the mortality benefit over NIV or standard oxygen.[7]

With the onset of the coronavirus disease 2019 (COVID-19) pandemic, the use of NIOS for hypoxemic respiratory failure has become even more controversial. Great trepidation surrounded NIOS use for patients with COVID-19 because of concern about aerosolization of viral particles and spread of disease to caregivers. Some centers used virtually no NIOS, preferring to intubate patients who needed more than standard oxygen via nasal cannula to minimize aerosolization,[8] whereas other centers used NIOS in the majority of hypoxemic patients with COVID-19 pneumonia. These differences were reflected in the many guidelines proffered by different organizations early during the pandemic, such as the Surviving Sepsis Campaign of the Society of Critical Care Medicine, which "suggested" use of HFNC as the initial modality in patients requiring more than standard lower flow oxygenation techniques,[9] and the World Health Organization, which gave a cautious recommendation to use NIOS in only "selected" patients.[10]

A few studies have reported experiences and outcomes of NIOS to treat COVID-19 pneumonia, including a prospective observational study involving 670 subjects from Italy treated with noninvasive respiratory support outside the ICU.[11] In that study, helmet CPAP was provided to 49% of the subjects, NIV using a face mask to 27%, and HFNC to 24%. Intubations rates were 25%, 28%, and 28%, and mortality rates were 30%, 30%, and 16% in the 3 groups, respectively, with no statistically significant differences. Another study from 4 ICUs in Paris indicated that, among 379 subjects requiring $\geq$ 3 L/min O_2 via nasal cannula to maintain an O_2 saturation $\geq$ 92%, 39% received HFNC within the first 24 h and the intubation rate was lower (55% vs 72%) than in those not receiving HFNC, whereas 28-d mortality was no different (21% vs 22%).[12] The authors concluded that HFNC could reduce the need for intubation but not mortality, and HFNC was as safe as standard oxygen therapy. In a more recent randomized controlled trial from 4 ICUs in Italy, 109 subjects with COVID-19 pneumonia and $P_{aO_2}/F_{IO_2} \leq 200$ received

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helmet NIV or HFNC.[13] The number of days without respiratory support, the major outcome variable, was not different between the groups (18 vs 20 d), intubation rate was lower in the helmet group (30% vs 51%), and the mortality rate was similar (24% vs 25%). Other than demonstrating that NIOS use for COVID pneumonia varies between institutions in both non-ICU and ICU settings and that it is probably as safe as other noninvasive approaches such as standard oxygen leading to intubation, studies to date do not provide definitive answers on relative safety and outcomes of NIOS compared to other approaches like initial standard oxygen followed by early invasive mechanical ventilation.

In the current issue of RESPIRATORY CARE, Menga et al[14] add to the accumulating data on use of NIOS for hypoxemic respiratory failure due to COVID-19 pneumonia with their prospective, observational cohort of 120 consecutive subjects admitted to the ICU, 85 (71%) of whom received first-line treatment with NIOS. Half of these subjects received helmet NIV, 28% received HFNC, and 22% were treated with face mask NIV. Of the 85 subjects treated with NIOS, 52 (61%) required endotracheal intubation within 28 d. After 1 h of NIOS, P_{aO_2}/F_{IO_2} was higher in 97% of subjects and was not predictive of subsequent intubation. Independent predictors of intubation were Simplified Acute Physiology Score II (SAPS II) $\geq$ 33 and lactate dehydrogenase $\geq$ 405, and the combination had a sensitivity and specificity for endotracheal intubation of 43% and 91%, respectively, and a positive predictive value of 88%.

The authors also compared 54 subjects from the current cohort with 54 historical controls from a previous similar study,[15] matched for age, SAPS II, P_{aO_2}/F_{IO_2}, and P_{aCO_2} upon enrollment. The intubation rate for the contemporary COVID-19 cohort was nearly twice that of the matched historical controls (59% vs 35%, $P = .02$). The authors concluded that first-line use of NIOS is common in patients with hypoxic respiratory failure due to COVID-19 pneumonia, and patients started on NIOS have a high risk of needing intubation.

Strengths of the study include the prospective design, the relatively large number of subjects compared to other reports on use of NIOS for patients with COVID-19, and propensity matching for the historical controls. There are numerous limitations as well, including the lack of randomized controls; the use of a single center, which precludes generalizability; and insufficient numbers to make observations about outcomes of the various NIOS methods used, which would have been of interest. Furthermore, the rate of intubation for subjects treated with NIOS is likely an overestimate because the denominator consists of patients admitted to the ICU, representing a sicker subpopulation of patients with COVID-19 pneumonia. In a contemporaneous study, Franco et al[11] reporting outcomes of subjects with COVID-19 pneumonia who were treated with NIOS outside the ICU. They observed an overall intubation rate of 27%, much lower than the current ICU cohort.

Questions must also be raised about the appropriateness of the cohort of historical controls consisting of a variety of non-COVID etiologies for ARDS. This historical study was performed between 17 and 19 y ago at 3 different centers in Italy, Spain, and the United States, not including the center in Italy from which the current cohort was derived. Practices were quite different then, with most patients receiving face mask NIV, some receiving helmet NIV, and none receiving HFNC, which wasn't available at the time. The authors appropriately eliminated HFNC from their present cohort for the historical comparison, which had a minimal effect on the intubation rate of the present cohort, dropping it from 61% to 59%.

Other concerns about the historical matching include the fact that the intubation rate of the historical study was at the low end of that reported in other studies at the time, which ranged up to two thirds.[16] It is also notable that the intubation rate for subjects treated with NIV in the more recent FLORALI study involving subjects who did not have COVID-19 was 50%, much closer to that in the current cohort. In addition, the intubation rate of the current cohort may have been higher due to pragmatic issues related to the pandemic, which placed enormous stresses on ICU bed availability and raised concerns about increased spread of disease using NIOS. This meant that only the sickest patients were admitted to the ICU, a population of patients presumably at higher risk for needing intubation, and the threshold for intubation may have been lower than that in the older cohort, which may have predisposed to the higher intubation rate. The propensity matching accounts for some of these concerns, but as the authors acknowledge, propensity matching cannot account for all potential confounders. There is also evidence that intubation rate may be dropping as the pandemic evolves. A recent piece by Torjesen[17] reported that the intubation rate of patients admitted to the ICU with COVID-19 pneumonia in the United Kingdom has dropped from 72% in the first surge (before August 31, 2020) to 44% since that time. This evolution over time in the management of ventilator support for COVID 19 pneumonia should be considered in interpreting results from the current cohort.

Despite these limitations, however, patients with hypoxemic respiratory failure due to COVID-19 do appear to differ in important ways from those with non-COVID-19 hypoxemic respiratory failure, often having long and complicated courses on the ventilator partly related to the "cytokine storm" associated with multi-organ system failure. Such complications cannot be managed with NIOS and likely contribute to the failure of NIOS in the patients who subsequently require intubation. These complications may also explain why P_{aO_2}/F_{IO_2} was not predictive of NIOS success in the current cohort of subjects, in contrast to its predictive utility in the historical cohort. It is unfortunate that the authors did not examine the utility of the ROX index,

defined as the ratio of S_{pO_2}/F_{IO_2} to breathing frequency, as a predictor, but this index may also have failed because it may not presage the occurrence of later multi-organ system failure.

The authors did note that the SAPS II score was predictive of outcome in the COVID-19 cohort, which is not surprising in that it reflects multi-organ system involvement, and it was predictive of the need for intubation in the historical cohort as well. They also identified elevation of lactate dehydrogenase, which, although nonspecific, may be indicative of the severity of the impending illness. With a positive predictive value for intubation of nearly 90% when combined, these indices deserve further examination and comparison with other potential predictors. Given the concern about excessive tidal volumes during NIV contributing to high tidal volumes and patient self-induced lung injury,[18] it would be of interest to examine breathing patterns in patients with COVID-19 as a predictor of outcome as well.

Despite more than a year of experience in dealing with the COVID-19 pandemic, we are still largely in the dark as to when to use NIOS as opposed to earlier intubation when treating acute respiratory failure due to COVID pneumonia and when to transition to invasive mechanical ventilation when a patient on NIOS isn't doing as well as desired. Some patients are clearly too ill for NIOS if they are severely hypoxemic at the start or if they develop multi-organ system failure during NIOS use, but there are some who exhibit a marginal respiratory status for lengthy periods of time, such that we agonize over the decision whether to proceed to intubation or not. A large controlled trial of subjects randomized to NIOS versus standard oxygen with intubation if needed would be desirable, but such a study is very challenging to implement in the face of a pandemic. The study by Menga et al[14] helps by demonstrating that P_{aO_2}/F_{IO_2} did not predict the need for intubation in subjects with COVID-19 pneumonia, whereas SAPS II and lactate dehydrogenase did. It also suggests that patients with ARDS related to COVID-19 pneumonia may be more prone to intubation that non-COVID forms and, most importantly, highlights that such patients must be monitored very cautiously to avoid delay of a needed intubation.

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REFERENCES

1. Stefan MS, Eckert P, Tiru B, Friderici J, Lindenauer PK, Steingrub JS. High flow nasal oxygen therapy utilization: 7-year experience at a community teaching hospital. Hosp Pract 2018;46(2):73-76.
2. Elliott MW. Non-invasive ventilation for acute respiratory disease. Br Med Bull 2004;72(1):83-97.
3. Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. Eur Respir J 2017;50(2):1602426.
4. Bellani G, Laffey JG, Pham T, Madotto F, Fan E, Brochard L, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. Am J Respir Crit Care Med 2017;195(1):67-77.
5. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2016;315(22):2435-2441.
6. Frat J-P, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372(23):2185-2196.
7. Ni YN, Luo J, Yu H, Liu D, Ni Z, Cheng J, et al. Can high-flow nasal cannula reduce the rate of endotracheal intubation in adult patients with acute respiratory failure compared with conventional oxygen therapy and noninvasive positive pressure ventilation? A systematic review and meta-analysis. Chest 2017;151(4):764-775.
8. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395(10239):1763-1770.
9. Alhazzani W, Evans L, Alshamsi F, Møller MH, Ostermann M, Prescott HC, et al. Surviving Sepsis Campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. Crit Care Med 2021;49(3):e219-e234.
10. Torres MB, Salles A, Cochran A. Recognizing and reacting to microaggressions in medicine and surgery. JAMA Surg 2019;154(9):868-872.
11. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. Eur Respir J 2020;56(5):2002130.
12. Demoule A, Vieillard Baron A, Darmon M, Beurton A, Géri G, Voiriot G, et al. High-flow nasal cannula in critically ill patients with severe COVID-19. Am J Respir Crit Care Med 2020;202(7):1039-1042.
13. Grieco DL, Menga LS, Cesarano M, Rosà T, Spadaro S, Bitondo MM, et al. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial. JAMA 2021. doi: CrossRef.
14. Menga LS, Delle CL, Bongiovanni F, Lombardi G, Michi T, Luciani F, et al. High failure rate of noninvasive oxygenation strategies in critically ill patients witrh acute hypoxemic respiratory failure due to COVID-19. Respir Care 2021;66(5):705-714.
15. Antonelli M, Conti G, Esquinas A, Montini L, Maggiore SM, Bello G, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 2007;35(1):18-25.
16. Jolliet P, Abajo B, Pasquina P, Chevrolet JC. Non-invasive pressure support ventilation in severe community-acquired pneumonia. Intensive Care Med 2001;27(5):812-821.
17. Torjesen I. Covid-19: when to start invasive ventilation is "the million dollar question". BMJ 2021;372:n121.
18. Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med 2017;195(4):438-442.