High-Flow Nasal Cannula: Where Does It Fit?

High-flow nasal cannula (HFNC) oxygen therapy is being examined as an alternative to standard oxygen therapy and noninvasive ventilation (NIV) in critically ill patients with hypoxemic respiratory failure and in mechanically ventilated patients at risk for re-intubation. A number of physiological benefits have been proposed for HFNC, including flow-dependent positive airway pressure and an alveolar recruitment effect.¹ In this issue of *RESPIRATORY CARE*, Lamb and coworkers² point out the limitations of available data supporting the use of HFNC in the setting of progressive hypoxemic respiratory failure and in the initial hours after extubation. This group provides additional data concerning the relevance of HFNC in these settings. I will briefly review physiologic and clinical statements regarding this therapy, placing them in the context of the paper presented in this issue of the Journal.

Physiologic Implications

HFNC is noninvasive respiratory support designed to deliver 30–60 L/min of heated humidified air and oxygen through specifically designed nasal prongs. This technology grew from work in preterm infants and pediatric patients and has recently been expanded to adults with acute hypoxemic respiratory failure.³ Physiologic benefits of HFNC continue to be investigated. In one report featuring HFNC, esophageal pressure changes during respiration were lower than with standard non-occlusive oxygen face-mask support, indicating that subjects had less inspiratory effort. The tidal volume change with differing esophageal pressure, an estimate of dynamic lung compliance, was significantly higher during HFNC, suggesting external ventilation support by the mandatory flow of HFNC during inspiration with improved lung mechanics. Changes in observed transpulmonary pressure also suggest decreased work of breathing.^{3,4}

Minute ventilation was also lower with HFNC than with standard non-occlusive face-mask oxygen support in these physiologic trials. On average, breathing frequency de-

creased with HFNC, whereas tidal volume did not change either at the global or regional level in the lung. Despite a decrease in minute ventilation, HFNC significantly

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improved oxygenation while pH and P_{CO_2} were stable. There was also significant correlation between the reduction in transpulmonary pressure and the change in minute ventilation during HFNC, suggesting that enhanced CO_2 clearance by washout of the upper airways reduced the inspiratory work of breathing or that HFNC reduced CO_2 production and associated ventilation needs.^{3,5} The relative reduction in transpulmonary pressure when subjects were transitioned from face-mask oxygen to HFNC was larger than the reduction of minute ventilation.

Lung volume, as reflected in this recent physiologic work, increased during HFNC both globally and in the dependent and nondependent lung regions. The increase in global gas content of the lungs was 50–60% of baseline tidal volume. This finding suggests that the generation of PEEP by HFNC improved oxygenation in the presence of unchanged tidal volume and reduced regional lung strain. Inhomogeneity of ventilation was reduced during HFNC. Perhaps most telling is the relationship between the reduction in minute ventilation and changes in transpulmonary pressure, suggesting that better CO_2 clearance may have a key role in reducing work of breathing.^{3,6}

HFNC may also affect ventilator-induced lung injury.^{7–9} A decrease in transpulmonary driving pressure was noted with inspiration on HFNC in prior studies. This observation appeared to correspond to an additional PEEP effect that resulted in a reduced tendency for lung collapse. Because higher driving transpulmonary pressure and derecruitment potentially aggravate lung injury, HFNC may reduce this risk. Increased end-expiratory lung volume produced by HFNC with unchanged tidal volume may reduce lung strain, which has been correlated with severity of ventilator-induced lung injury. A decrease in the inhomogeneity of ventilation indirectly suggests that there may be fewer or smaller sites of alveolar collapse, which can potentially reduce the risk of focal multiplication of alveolar wall tension and ultrastructural injury. Thus, it is possible that HFNC, in addition to supporting oxygenation, may affect deter-

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minants of ventilator-induced lung injury such as lung stress, strain, and inhomogeneity of gas distribution.

HFNC in Acute Respiratory Failure

Acute respiratory failure is an important complication, causing up to 30% of ICU admissions and up to 50% of ICU patient deaths. It has been reported that approximately 60% of patients with acute respiratory failure require endotracheal intubation and mechanical ventilation. Unfortunately, invasive mechanical ventilation has been associated with various adverse events, including hospital mortality as high as 30%.¹⁰⁻¹²

NIV is a commonly used means of respiratory support in patients with acute respiratory failure. This method avoids the use of the endotracheal tube and offers improved clinical outcomes in appropriately selected patients. However, there are hazards with NIV, such as skin damage, eye irritation, interface intolerance, and diet and expectoration interruptions.¹³ These hazards sometimes limit the application of NIV in clinical practice. Thus, substitutes for NIV that demonstrate similar efficacy but fewer adverse events are of interest. HFNC is a leading candidate to supplement or replace NIV in selected patients. Because of the clinical efficacy of HFNC, as well as its easy application and improved patient tolerance, physicians are investigating the potential role of HFNC in improving clinical outcomes in adults with acute respiratory failure. Contradictory conclusions have been drawn in multiple trials, however.¹⁰

A recent systematic review was conducted to examine the effectiveness of HFNC relative to conventional oxygen therapy and NIV.¹⁰ In this extensive meta-analysis, HFNC decreased the need for endotracheal intubation in adult subjects with acute respiratory failure in a manner similar to NIV. However, HFNC was not associated with improvement in ICU mortality or a decrease in ICU stay compared with NIV or conventional oxygen therapy. HFNC was associated with a reduced need for endotracheal intubation in comparison to conventional face-mask oxygen therapy. These observations may be the result of multiple factors, some of which are described above. HFNC was also better tolerated in subjects with acute respiratory failure.

An intriguing study examining the physiologic impact of HFNC and NIV comes from a group of subjects evaluated for intubation in the setting of hypoxemia in the critical-care unit.¹⁴ In this study, a small group of subjects receiving NIV via mask were randomized between this therapy with and without HFNC. The ultimate rationale for this study was to examine the combination of HFNC with NIV in comparison to conventional NIV for oxygenation before intubation in hypoxemic patients. In this trial, NIV plus HFNC decreased the risk of desaturation asso-

ciated with intubation episodes in critically ill hypoxemic subjects in the ICU. The primary outcome studied was minimal oxygen saturation obtained during the intubation procedure.

The results obtained did not demonstrate any safety concerns and showed that the combination of HFNC and other NIV was more effective in protecting oxygen saturation values during intubation than oxygenation using NIV alone.¹⁴ Intriguing in this small study was the extensive provision for blinding the study so that the impact of the combined technique versus isolated NIV could be discerned. Technical considerations, particularly in a small study population, could explain results obtained, such as gas leak associated with the combination of placebo HFNC tubing and a face-mask NIV circuit. However, while this work provides a model to be considered for safer intubation in the severely hypoxemic patient, it also suggests that even where conventional NIV is employed, the HFNC technique offers supplemental benefit in protection of patient oxygenation.

Weaning

Respiratory failure following extubation after surgical procedures or prolonged mechanical ventilation often requires re-intubation. While prolonged mechanical ventilation in the ICU is associated with mortality, re-intubation is also associated with increased risk of mortality and respiratory complications, including aspiration and pneumonia. Thus, there is interest in the identification of strategies to support patients at risk for postextubation respiratory failure and to reduce the need for re-intubation. Two contemporary options include NIV via a sealed mask and, more recently, HFNC therapy. Both strategies avoid invasion of the upper airway and its attendant complications.^{15,16}

Through a combination of variable flow, mask seal, and expiratory valves, NIV may deliver CPAP or bi-level positive airway pressure. In the bi-level mode, higher pressure during inspiration is combined with a lower pressure during expiration, similar to what is typically provided by the ventilator with PEEP. In other words, inspiratory and expiratory pressures are independently adjusted. By applying extrinsic PEEP, NIV may counterbalance the autoPEEP phenomenon in patients with COPD and reopen flooded alveoli in acute pulmonary edema secondary to heart failure, resulting in improved gas exchange and lung compliance. In addition, adding inspiratory pressure during NIV assists inspiration and reduces the work of breathing, which can forestall the onset of respiratory muscle fatigue. For these reasons, NIV is recommended for patients who present with respiratory failure in the emergency department, particularly if attributable to COPD or acute cardiogenic pulmonary edema.¹⁷ Unfortunately, patients frequently tolerate NIV poorly because of mask discomfort or claustro-

phobia, which may limit the number of hours per day that mask ventilation can be employed.¹³

HFNC is humidified and delivered at body temperature to avoid cooling and desiccation of the nasal mucosa, and most patients perceive this to be more comfortable than standard high-flow oxygen masks or NIV.¹⁸ HFNC gas flows match the high spontaneous inspiratory flows generated by patients with shortness of breath, reduce entrainment of room air, and permit delivery of more consistent fractions of inspired oxygen, which can be adjusted up to 100%. HFNC flushes out anatomical dead space in the upper airway, improving respiratory efficiency and reducing the breathing frequency. Furthermore, HFNC delivers a low level of positive airway pressure (0.5–1 cm H₂O per each 10 L/min increment) to recruit alveoli and increase end-expiratory lung volume. Humidification of this high-flow gas also promotes mobilization of secretions, and the less obtrusive nasal prongs permit unimpeded speech and eating. Thus, unlike other forms of noninvasive respiratory support, HFNC is well tolerated and may be used continuously for days.¹⁸

Studies can be found to support a role for NIV after extubation, including avoidance of re-intubation, decreased stay, and reduced infectious complications. We are also beginning to obtain data related to the optimal role for HFNC in patients with various forms of respiratory failure, although relatively few studies compare high-flow nasal oxygen to NIV.¹⁹ One trial in subjects who underwent cardiac surgery suggests that high-flow nasal oxygen is noninferior to NIV in reducing the rate of treatment failure, defined as re-intubation or differences in comfort, tolerance of therapy, or critical-care-unit mortality.

A recent issue of the *Journal of the American Medical Association* includes an article about a trial comparing NIV via mask to standard face-mask oxygen therapy, and another article about a trial comparing HFNC oxygen to standard face-mask oxygen therapy.¹⁵ The study of Jaber et al¹⁷ compared NIV via face-mask with standard oxygen therapy among nearly 300 subjects undergoing abdominal surgery. NIV reduced the 7-d re-intubation rate and increased ventilator-free days at 30 days compared with standard oxygen therapy. NIV also reduced healthcare-associated infections, but not mortality or hospital stay. Infection reduction is consistent with NIV's theoretical advantage of avoiding prolonged endotracheal intubation.

The same issue included an article by Hernández and co-workers.¹⁸ These authors examined the role of HFNC in reducing 72-h re-intubation after extubation. This study recruited > 500 subjects deemed at low risk for extubation failure by virtue of passing a spontaneous breathing trial and the absence of high-risk factors like older age, obesity, inability to manage secretions, or the need for > 7 d of invasive mechanical ventilation. Subjects randomized to receive HFNC had a lower re-intubation rate at 72 h com-

pared to those receiving standard oxygen therapy. Time to re-intubation, ICU stay, and mortality rates were not significantly different between the HFNC and the standard face-mask oxygen groups.

These important studies add to evidence that noninvasive approaches may have a role in reducing respiratory failure and the need for re-intubation in the post-surgical or general postextubation setting. The study designs are robust, and subject groups are large. Both trials have specified intubation criteria and minimize crossovers to alternative therapies. In addition, both trials attempt to account for the effects of potential confounders by stratifying for age, surgical site (if appropriate), and type of analgesia.

Both of these trials have weaknesses.¹⁹ Jaber et al¹⁷ included more subjects with COPD in the NIV group than in the standard oxygen-therapy group. COPD patients can be expected to have better outcomes with NIV based on previously published data. al¹⁷ Hernández and coworkers¹⁸ primarily included subjects with postsurgical and neurologic conditions, which pose secretion-clearance challenges that favor better outcomes with HFNC. Thus, both studies may have limitations based on the application of these practices to all intensive-care patients. In addition, these trials were performed in centers of excellence; less experienced centers might not be able to replicate these outcomes. A universal problem with these types of studies is the impossibility of blinding. Even if a sham mask is applied, clinicians can distinguish between groups by appearance or noise made by various devices.

What's New?

In this issue of *RESPIRATORY CARE*, Lamb and coworkers examine clinical application of HFNC in subjects following extubation and as an escalation therapy prior to intubation in individuals with progressive respiratory insufficiency.² Historical controls were employed. The first study cohort had received mechanical ventilation for at least 24 h and was extubated directly to HFNC. A decrease in Gram-negative infections was identified along with reduced bronchodilator use. While rigorous data are not available to explain these findings, the authors appropriately report that Gram-negative infections have a significant impact on respiratory morbidity in the critical-care setting. Early use of HFNC clearly could facilitate secretion clearance with a decreased quantity of pathogens and time of exposure to Gram-negative organisms. In addition, reduced bronchodilator use was seen in the HFNC group, consistent with the humidification provided by the HFNC technology. While the investigators note that failed extubation rates were nearly identical across groups, it would be interesting to investigate whether the ultimate impact of re-intubation, typically thought to be a marker of poor outcome, is less severe in patients extubated to HFNC, where

secretion clearance and airway maintenance may be improved.

The second cohort of subjects was evaluated with an HFNC protocol employed as oxygen requirements escalated prior to intubation.² HFNC subjects moved more rapidly to intubation when this technology failed, and there was a trend toward fewer hours utilizing HFNC in subjects who required increasing oxygen therapy. When intubated, subjects who were on HFNC required significantly fewer days in the ICU and in hospital. Potential advantages of HFNC highlighted in this cohort of subjects are the potential for reduced sedation and improved monitoring as patients have increased opportunity to interact with the care team. Thus, earlier identification of the patient at risk for oxygenation failure should be present. We do not have specific sedation and monitoring data on these subjects, but I note that in the hospital utilized for this single-center trial, HFNC is not used outside the critical-care setting.

Like many important studies, this report does not feature rigorous statistical design and randomization. Thus, larger studies with a larger data set will ultimately be required. This pathfinding work does, however, demonstrate potential advantages of HFNC in both the patient with progressive respiratory insufficiency and in the setting of discontinuation of mechanical ventilation. Unlike the carefully scripted studies described earlier in this brief review, the work of Lamb et al² reflects the results of routine bedside application of HFNC in a heterogeneous patient population. This study design will enhance the relevance of this work.²⁰

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