FOCUSED REVIEW

High-Flow Nasal Cannula Oxygen in Adults: An Evidence-based Assessment

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Abstract

High-flow nasal cannula oxygenation has distinct advantages over other oxygen devices because of its unique effects on respiratory physiology. In particular, adjustable oxygen delivery and flow-dependent carbon dioxide clearance reduce work of breathing and better match inspiratory demand during respiratory distress. Historically, few studies had evaluated whether the physiologic effects of these devices translated into clinical benefit. However, recent publications have begun to address this knowledge gap. High-flow nasal cannula oxygenation has been shown to have similar, and in some cases superior clinical efficacy compared with conventional low-flow oxygen supplementation and noninvasive positive pressure ventilation in acute hypoxemic respiratory failure. High-flow nasal cannula oxygenation also prevents reintubations in medical and postoperative surgical populations, provides preoxygenation for laryngoscopy, and supports oxygenation during bronchoscopy. This review examines the evidence for high-flow nasal cannula oxygenation use in adults, including a focus on the unique effects of high flow on respiratory physiology and keys for tailoring flow for specific clinical scenarios.

Keywords: respiratory failure; hypoxia; high-flow nasal cannula; noninvasive ventilation

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High-flow nasal cannula (HFNC) oxygenation has become an increasingly popular therapy for hypoxemic respiratory failure. This review evaluates evidence for HFNC use in adults, with a particular focus on respiratory physiology, clinical indications, device titration, and concepts to guide future research.

Physiologic Effects of High-Flow Nasal Cannula Oxygenation

Alveolar oxygen delivery depends on supplemental oxygen flow rate, the fraction of inspired oxygen ($F_{I_{O_2}}$) delivered in supplemental flow, the device's interface with the patient, and inspiratory demand (1, 2). Conventional low-flow devices (e.g., nasal cannula or simple face mask) provide 100% $F_{I_{O_2}}$ at a maximum of 15 liters per minute. Even during quiet breathing, inspiratory flow rates are approximately 30 liters per minute, which exceeds supplemental oxygen flow (3). Thus, room air containing 21% $F_{I_{O_2}}$ is entrained to meet inspiratory demand, which dilutes the total $F_{I_{O_2}}$ of the inspiratory flow. During respiratory distress, flows reach 100 liters per minute or more, resulting in entrainment of much larger volumes of room air that further reduce delivered $F_{I_{O_2}}$.

Intermediate-flow devices, such as Venturi masks, also suffer from this phenomenon. Venturi masks provide predictable $F_{I_{O_2}}$ by regulating the ratio of supplemental oxygen to room air (4). When $F_{I_{O_2}}$ requirements are low, Venturi masks provide higher flow because more room air is entrained through large ports on the device (e.g., at 28% $F_{I_{O_2}}$, total flow is ∼44 L/min) (Figure 1). However, to achieve higher $F_{I_{O_2}}$, less room air is entrained to increase the ratio of supplemental oxygen to room air. As a consequence, maximum flow is reduced (e.g., at 60% $F_{I_{O_2}}$, total flow is ∼24 L/min). Thus, patients often entrain additional room air around the mask to meet inspiratory demand, which causes the $F_{I_{O_2}}$ of the inspired flow to fall.

The HFNC overcomes flow limitations of low- and intermediate-flow devices by delivering up to 60 liters per minute of heated, humidified gas via nasal prongs (Figure 1) (5). An oxygen blender connected to the circuit enables precise titration of $F_{I_{O_2}}$ ranging from 21 to 100%, independent of flow. To ensure stable $F_{I_{O_2}}$ delivery to alveoli, device flow must meet or exceed the patient's inspiratory flow to minimize room air entrainment (6).

Because inspiratory flow is not routinely measured in nonintubated

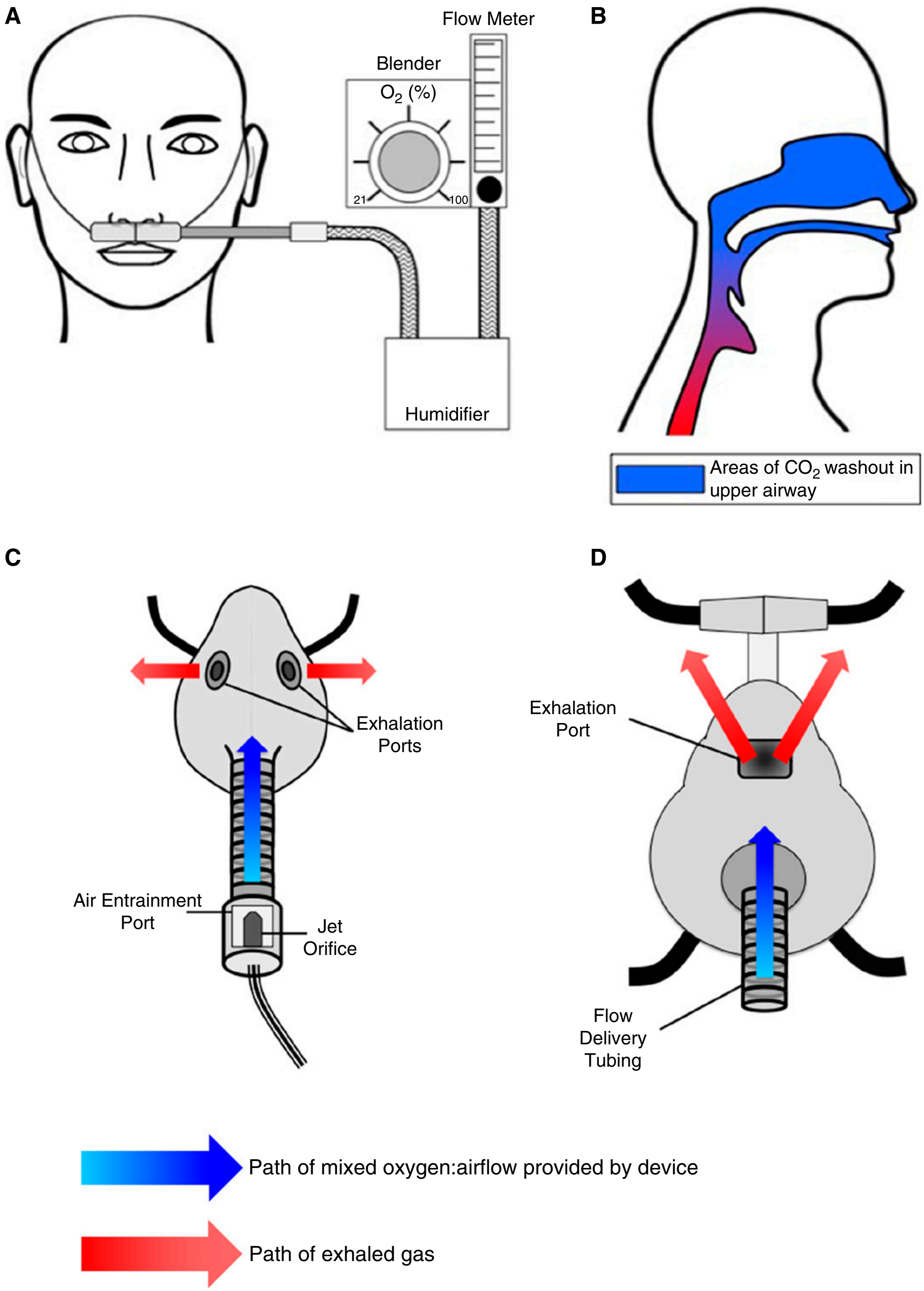

Figure 1. Comparison of high-flow nasal cannula oxygenation with Venturi mask and noninvasive positive pressure ventilation. (*A*) The high-flow nasal cannula circuit consists of a flow meter and oxygen–air blender connected to a humidifier. Flow rates up to 60 liters per minute are delivered to the nasal cannula via a heated circuit. The fraction of inspired oxygen ($F_{I_{O_2}}$) can be titrated from 21 to 100% independent of the flow rate. (*B*) High-flow nasal cannulas wash CO_2 out of the upper airway (illustrated in blue), resulting in reduced anatomic dead space and improved work of breathing. Because CO_2 clearance is flow dependent, it is desirable to target the highest flow tolerated by patients. (*C*) Venturi masks provide fixed $F_{I_{O_2}}$ (blue arrow) by regulating the ratio of entrained room air that mixes with 100% oxygen delivered by the inspiratory jet. Exhaled gas containing CO_2 is released via ports on the sides of the face mask (red arrows). (*D*) Noninvasive positive pressure ventilators deliver pressure-targeted breaths by varying the inspiratory flow (blue arrow). $F_{I_{O_2}}$ and inspiratory pressure are independently set. Masks must be tightly secured to the patient's face to limit air leaks and room air entrainment around the mask seal. Mask design varies by manufacturer. Full face masks (pictured) release exhaled CO_2 via an exhalation port.

patients, initial device settings are often selected on the basis of qualitative assessments of the patient's respiratory demand (e.g., respiratory rate, work of breathing, accessory muscle use) and to achieve a desired oxygen saturation as measured by pulse oximetry (Sp_{O_2}). However, this approach fails to account for the ability of the HFNC to also wash carbon dioxide (CO_2) out of the upper airways. Indeed, unlike low-flow nasal cannulas and masks that solely support oxygenation, HFNC produces flow-dependent CO_2 clearance that reduces anatomic dead space and leads to improved work of breathing and lower respiratory rates (Table 1). This effect was elegantly demonstrated by Mauri and colleagues in a recent study of hypoxemic patients with arterial partial pressure of oxygen (Pa_{O_2}) to FI_{O_2} ratios less than 300 (7). HFNC set at 40 liters per minute significantly reduced work of breathing and respiratory metabolic demand compared with oxygen delivered by face mask at 12 liters per minute. Patients with an elevated arterial partial pressure of carbon dioxide (Pa_{CO_2}) at baseline had the greatest improvement in work of breathing. Thus, patients with hypercarbia in addition to hypoxemia appear to gain the greatest benefit from the combination of upper airway CO_2 clearance and decreased CO_2 production from reduced metabolic demand. Achieving sufficiently high flow is critical to maximizing CO_2 washout. Increasing flows from 15 to 45 liters per minute tripled the reduction in anatomic dead space, from 20 to 60 ml (8). Therefore, when the goal is to prevent intubation, it is desirable to target the highest flow tolerated by the patient to reduce work of breathing while separately titrating FI_{O_2} to achieve the desired Sp_{O_2}.

HFNC also improves gas transfer and increases lung volumes. Using electrical impedance tomography, Corley and colleagues found substantially increased end expiratory lung volumes with HFNC compared with low-flow devices (9), a finding corroborated by Mauri's study (7). This effect was greatest for obese patients. Because end-expiratory lung volumes are a reflection of functional residual capacity, increases in volume suggest that HFNC use results in alveolar recruitment. Thus, more lung units are available to participate in gas exchange. Alveolar recruitment may result from generation of positive airway pressure, although the magnitude of this effect is controversial. Whereas 45 liters per minute generated a mean pressure of 2.0 cm H_2O in the trachea with the mouth closed, only 0.6 cm H_2O was generated with the mouth open. The highest individual mean pressure recorded at 45 liters per minute was only 2.3 cm H_2O (6). Similarly, 50 liters per minute produced 3.3 cm H_2O in the nasopharynx with the mouth closed, but only 1.7 cm H_2O with the mouth open (10). Because most patients in respiratory distress breathe through an open mouth, generation of positive pressure by HFNC may be mitigated in many patients. Patient position, body habitus, and distribution of lung disease also impact the ability of HFNC to recruit alveoli. For example, HFNC produced regional lung recruitment predominantly in the ventral lungs of healthy subjects when supine, but homogeneous improvements when subjects were prone (11). In diseased lungs with heterogeneous airflow and alveolar mechanics, recruitment was unpredictable, which likely contributes to variability in the magnitude of the treatment effect for individual patients.

Noninvasive positive pressure ventilation (NIV) is also commonly used for alveolar recruitment. NIV provides pressure-targeted breaths by varying inspiratory flow throughout the respiratory cycle. Positive end-expiratory pressure and FI_{O_2} are titrated independently. To maintain positive pressure, the NIV mask must be firmly secured to the patient's face, which hinders communication and secretion clearance. In this circumstance, HFNC offers additional advantages. The HFNC device interface allows for better patient communication, less anxiety and claustrophobia, and superior comfort compared with NIV and face masks (5, 12–14). While the patient is receiving HFNC oxygenation, oral suctioning and expectoration can occur. Airway clearance is also improved by the delivery of heated, humidified gas that enhances epithelial mucociliary function (15, 16) and optimizes airflow conductance, which can reduce the metabolic cost of breathing (17).

Table 1. Physiologic benefits of high-flow nasal cannula compared with conventional low-flow oxygenation

Improved oxygenation
Decreased anatomic dead space owing to washout of upper airway
Decreased metabolic cost of breathing/reduced carbon dioxide generation
Generation of positive nasopharyngeal and tracheal airway pressure
Improved work of breathing
Preconditioning of inspired gas (heated and humidified)
Better secretion clearance
Superior comfort
Reduced room air entrainment

Acute Hypoxemic Respiratory Failure

Acute hypoxemic respiratory failure is a primary reason for instituting HFNC therapy, although until recently the effect of HFNC on intubation rates and mortality had not been evaluated in a prospective, randomized study. The multicenter FLORALI (Clinical Effect of the Association of Noninvasive Ventilation and High-Flow Nasal Oxygen Therapy in Resuscitation of Patients with Acute Lung Injury) trial addressed these questions by comparing HFNC with conventional low-flow oxygen and NIV (Table 2) (18). Adults with no prior history of lung disease who presented with a respiratory rate greater than 25 breaths per minute, a Pa_{O_2}/FI_{O_2} ratio less than 300 on 10 liters per minute or more of oxygen, and a Pa_{CO_2} below 45 mm Hg were randomized to receive HFNC therapy (50 L/min with FI_{O_2} titrated to Sp_{O_2} >92%), oxygen via a nonrebreather face mask (⩾10 L/min for Sp_{O_2} >92%), or NIV (inspiratory pressure titrated to 7–10 ml/kg tidal volume, expiratory pressure 2–10 cm H_2O, and FI_{O_2} titrated for Sp_{O_2} >92%). Three-fourths of patients had pneumonia as their primary diagnosis. Ultimately, intubation rates were similar between treatments. However, owing to fewer than expected intubations overall, the study was underpowered for this outcome. Secondary outcomes included ventilator-free days and 90-day mortality, which were substantially reduced in patients receiving HFNC compared with conventional oxygen

Table 2. Prospective trials evaluating high-flow nasal cannula oxygenation in medical patients

Study	Design/*N*	Patients	Comparison	Outcomes
Acute hypoxemic respiratory failure				
FLORALI Frat and colleagues, 2015 (18)	RCT 310	Pa_{O_2}/FI_{O_2} ≤300	HFNC 50 L/min vs. COT or NIV	Fewer intubations with HFNC (38%) than with COT (47%) and NIV (50%) Lower 90-d mortality with HFNC
HOT-ER Jones and colleagues, 2016 (19)	RCT 303	Sp_{O_2} ≤92% and RR ≥22 breaths/min Admitted to ED	HFNC 40 L/min vs. COT	5.5% of HFNC vs. 11.6% of COT intubated within 24 h ($P = 0.053$) No difference in 90-d mortality
Immunosuppressed				
Coudroy and colleagues, 2016 (36)	Observational cohort 115	Pa_{O_2}/FI_{O_2} ≤300 RR ≥25 breaths/min	HFNC 50 L/min vs. NIV	Fewer intubations with HFNC than with NIV (35 vs. 55%) Lower 28-d mortality with HFNC (20 vs. 40%)
Frat and colleagues, 2016 (34)	*Post hoc* study of RCT 82	Pa_{O_2}/FI_{O_2} ≤300	HFNC 50 L/min vs. COT or NIV	31% of HFNC, 43% of COT, and 65% of NIV intubated by 28 d Age and NIV use as first-line therapy independently associated with need for intubation
Lemiale and colleagues, 2015 (80)	RCT 100	>6 L/min COT or symptoms of respiratory distress	HFNC 40–50 L/min vs. Venturi mask with 60% FI_{O_2}	No difference in intubations or comfort HFNC applied for only 2 h
Lemiale and colleagues, 2017 (37)	*Post hoc* study of RCT 353	Pa_{O_2} <60 mm Hg RR >30 breaths/min or respiratory distress	Propensity-matched analysis of HFNC 40 L/min (10–50) vs. COT	No difference in intubations No difference in 28-d mortality
Prevention of reintubation				
Hernández and colleagues, 2016 (52)	RCT 527	Successfully passed SBT Low risk for reintubation	HFNC 30 L/min vs. COT	Fewer reintubations within 72 h with HFNC (4.9%) than with COT (12.2%) No difference in time to reintubation
Hernández and colleagues, 2016 (53)	RCT 604	Successfully passed SBT High risk for reintubation	HFNC 50 L/min vs. NIV	Similar reintubation rates (22.8% in HFNC vs. 19.1% in NIV) over 72 h Less respiratory failure overall in HFNC (26.9% vs. 39.8%) More adverse events with NIV
Maggiore and colleagues, 2014 (51)	RCT 105	Pa_{O_2}/FI_{O_2} ≤300 at time of extubation	HFNC 50 L/min vs. Venturi mask	HFNC reduced desaturations, reintubations, and NIV Improved comfort with HFNC
Tiruvoipati and colleagues, 2010 (12)	Randomized crossover 42	Successfully passed SBT	HFNC → HFFM or vice versa 30 L/min	No difference in RR or gas exchange Improved comfort with HFNC
Palliative				
Peters and colleagues, 2013 (43)	Prospective cohort 50	Do-not-intubate status, in respiratory distress	HFNC 30–60 L/min, no comparison	HFNC improved RR and oxygenation

Definition of abbreviations: COT = conventional low-flow oxygen therapy; ED = emergency department; FI_{O_2} = fraction of inspired oxygen; FLORALI = Clinical Effect of the Association of Noninvasive Ventilation and High Flow Nasal Oxygen Therapy in Resuscitation of Patients with Acute Lung Injury; HFFM = high-flow face mask; HFNC = high-flow nasal cannula; NIV = noninvasive positive pressure ventilation; Pa_{O_2} = arterial partial pressure of oxygen; RCT = randomized controlled trial; RR = respiratory rate; SBT = spontaneous breathing trial; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

therapy and NIV. In a *post hoc* analysis, investigators also found that HFNC reduced intubations in the subgroup with a Pa_{O_2}/FI_{O_2} ratio below 200. The difference in 90-day mortality was due to a higher incidence of refractory shock in the conventional oxygen and NIV groups, leading some to question whether antimicrobial therapy was adequate, particularly because community-acquired pneumonia was the most common admitting diagnosis. The authors who reported the FLORALI results contended that antimicrobial therapy was appropriate in all three groups (97% in HFNC, 100% in conventional oxygen, and 94% in NIV). The adequacy of the NIV protocol has also been challenged because NIV was applied for a median of only 8 hours per day, possibly resulting in undertreatment. On the contrary, because HFNC was provided between NIV sessions, this protocol appears to reinforce the negative contribution of NIV compared with HFNC alone. Finally, the time until intubation was similar between HFNC and NIV, indicating that treatment outcomes were not influenced by delays in intubation.

In contrast to FLORALI, researchers in a second randomized trial of early HFNC initiation in the emergency room concluded that HFNC was not superior to conventional oxygen (19). The HOT-ER study investigators randomized 322 emergency room patients with hypoxemia (Sp_{O_2} ≤92% on room air) to HFNC (40 L/min with $F_{I_{O_2}}$ titrated on the basis of clinical need) or conventional oxygen (1–15 L/min). HFNC use resulted in lower rates of intubation after 24 hours (5.5% for HFNC vs. 11.6% for oxygen), although this difference did not reach statistical significance ($P = 0.053$). Mortality at 90 days was similar between groups (21.2% for HFNC vs. 17.4% for oxygen). The conflicting results of the HOT-ER and FLORALI trials likely relate to key differences in study design and patient characteristics. Whereas pneumonia was the most common admitting diagnosis in the FLORALI trial, only one-fourth of patients in the HOT-ER study had pneumonia. Over half of HOT-ER subjects presented with chronic obstructive pulmonary disease, asthma, or heart failure; patients with these diagnoses were excluded from the FLORALI study. FLORALI required 48 hours of continuous HFNC, whereas HOT-ER did not specify HFNC use after subjects left the emergency room, possibly leading to insufficient HFNC treatment. HOT-ER also did not compare HFNC with NIV. In addition, it is possible that differences in high-flow settings between the studies impacted treatment outcomes. Specifically, flow was set 10 liters per minute higher in FLORALI than in HOT-ER. Although this difference was small, it may have contributed to better CO_2 clearance in FLORALI subjects, leading to improved work of breathing and ultimately fewer intubations.

Overall, these trials build on prior nonrandomized studies that cumulatively support HFNC use for hypoxemic respiratory failure (5, 20–26) (Table 2). Authors of a recent meta-analysis of these studies that included over 3,000 subjects agreed. HFNC reduced the need for endotracheal intubation compared with conventional oxygen and NIV (odds ratio, 0.60; 95% confidence interval, 0.41–0.86) (27) and should be considered as first-line therapy for patients with acute hypoxemic respiratory failure.

Acute Hypoxemic Respiratory Failure in Immunosuppressed Patients

Immunosuppressed patients with hypoxemic respiratory failure who require mechanical ventilation have an especially high mortality (28, 29). NIV is recommended as first-line therapy (30) on the basis of two studies suggesting that NIV reduces intubations (31, 32) and mortality (32) compared with conventional oxygen. However, newer data raise doubts about the benefits of NIV. Specifically, Lemiale and colleagues found no difference in 28-day mortality between NIV and conventional oxygen in immunosuppressed patients (33). Furthermore, a *post hoc* analysis of the FLORALI trial suggested that NIV increased intubations and mortality compared with HFNC or conventional oxygen in immunosuppressed patients (34).

Several other studies corroborate the benefits of HFNC over NIV in immunosuppressed populations, as suggested by FLORALI. In a retrospective study of cancer patients, HFNC use was associated with lower 28-day mortality compared to patients treated with standard oxygen and/or NIV (35% vs. 57%) (35), and it was found in a prospective observational study to reduce intubations (35% vs. 55%) and mortality (20% vs. 40%) compared with NIV when used as first-line therapy (36). However, HFNC was ineffective as a rescue therapy after NIV or conventional oxygen failure (37), suggesting that the benefits of HFNC are greatest with early application of the device. The benefits of HFNC may also apply to lung transplant recipients. HFNC was associated with fewer intubations (59% vs. 89%) and lower hospital mortality (50% vs. 83%) compared with face mask oxygen in lung transplant recipients who required readmission to the intensive care unit (38). Furthermore, similar to its effects in other populations, HFNC was found to reduce dyspnea and respiratory rates in immunosuppressed patients (39–42). Thus, HFNC can provide effective palliation, even for those patients with advanced malignancies who have been designated as “do not intubate” (43, 44).

Predictors of High-Flow Nasal Cannula Treatment Failure in Patients with Acute Respiratory Failure

The decision to intubate and mechanically ventilate patients who show signs of progressive respiratory failure while on HFNC therapy remains a challenging clinical dilemma. Timely intubation is critical because unnecessarily delaying intubation beyond 48 hours for patients on HFNC was associated with increased mortality and prolonged mechanical ventilation (45). Signs that portend the need for mechanical ventilation include persistently high respiratory rates (22), ongoing hypoxemia, thoracoabdominal asynchrony (e.g., abdominal breathing), and the presence of nonpulmonary organ failure (46). However, none of these signs reliably identifies patients who should be intubated. Roca and colleagues attempted to address this challenge by developing a clinical index to identify patients on HFNC who ultimately require mechanical ventilation (47). The respiratory rate–oxygenation (ROX) index, defined as the ratio of $Sp_{O_2}/F_{I_{O_2}}$ to respiratory rate, was evaluated prospectively in patients with acute respiratory failure due to pneumonia. These authors concluded that a ROX index greater than 4.88 after 12 hours of HFNC therapy indicated that a patient was unlikely to need mechanical ventilation (positive predictive value, 89%). In contrast, no scoring threshold reliably predicted which patients would ultimately require intubation. Therefore, calculating the ROX index at 12 hours may be useful in determining who can safely continue HFNC therapy, but it cannot be used to identify for whom HFNC therapy will fail. Furthermore, it is unclear whether the ROX index can be applied in patients with respiratory failure due to causes other than pneumonia, and it cannot be used to predict outcomes at time points before 12 hours. Determining which patients require intubation, and when, continues to require a high degree of clinical judgment. Clinicians may benefit from prospectively defining intubation criteria to aid in clinical decision making. For example, in the FLORALI study, researchers initiated mechanical ventilation if subjects had ongoing hemodynamic instability, declining mental status, or worsening respiratory failure (e.g., respiratory rate, >40 breaths/min; pH, <7.35; Sp_{O_2}, <90% for 5 min) (18). Researchers in future studies should continue to seek early clinical signs that identify patients who will benefit from mechanical ventilation rather than continuation of HFNC.

Preventing Reintubations

NIV reduces reintubations in specific high-risk subgroups (48, 49), but not in critically ill patients overall (50). In contrast, HFNC may offer benefit across a spectrum of critical illness. For example, Maggiore and colleagues found that applying 50 liters per minute of HFNC for 48 hours after extubation substantially reduced NIV use and reintubations compared with a Venturi mask (3.8% vs. 21.2%) in patients who had passed a spontaneous breathing trial, but whose Pa_{O_2}/FI_{O_2} ratio was less than 300 (51). HFNC improved secretion clearance, prevented hypoxemia, and lowered respiratory rates, Pa_{CO_2}, and dyspnea scores (12, 13). Similarly, 30 liters per minute of HFNC delivered for 24 hours after extubation reduced reintubations versus conventional oxygen (4.9% vs. 12.2%) in low-risk patients and improved secretion clearance, with a number needed to treat of 14 to prevent one reintubation (52). Despite these results, routine application of HFNC for all low-risk patients is not recommended without careful consideration of the local case mix and existing rates of reintubation for individual intensive care units.

In patients at high risk for reintubation, HFNC delivered at 50 liters per minute after extubation had efficacy similar to NIV (titrated for respiratory rate <25 breaths/min, pH >7.35, and Sp_{O_2} >92%). After 72 hours, 22.8% of patients in the HFNC group were reintubated versus 19.1% in NIV (53). High-risk criteria included age greater than 65 years and at least one of the following: *1*) heart failure as the primary indication for intubation, *2*) moderate to severe chronic obstructive pulmonary disease, *3*) Acute Physiology and Chronic Health Evaluation II score greater than 12, *4*) body mass index (BMI) greater than 30 kg/m^2, *5*) limited airway patency, *6*) inability to manage secretions, *7*) more than two comorbidities, or *8*) mechanical ventilation for more than 7 days. HFNC was associated with a lower incidence of respiratory acidosis (pH <7.35) and improved secretion clearance, and it was better tolerated than NIV. Most subjects used HFNC for 24 hours after extubation per protocol, whereas NIV was tolerated for an average of only 14 hours, with 42% experiencing adverse events prompting treatment discontinuation. The authors acknowledged that their high-risk inclusion criteria have not been prospectively validated; yet, their results suggest that HFNC is beneficial, particularly when secretion clearance is a priority or in the case of NIV mask intolerance.

Postoperative Respiratory Failure

Cardiothoracic Surgery

Respiratory failure after cardiothoracic surgery is associated with increased mortality (54, 55). NIV is recommended to prevent reintubation on the basis of moderate (grade 2) evidence (56). Recent studies suggest that HFNC may have a similar benefit (Table 3). Stephán and colleagues randomized cardiothoracic surgery patients at high risk for reintubation to 50 liters per minute of HFNC or NIV (inspiratory pressure titrated to 8 ml/kg tidal volume, expiratory pressure set at 4 cm H_2O, FI_{O_2} titrated to Sp_{O_2} 92 to 98%) after extubation (57). NIV was delivered for 2 hours initially, then for 1 of every 4 hours with conventional oxygen administered between sessions. Rates of treatment failure, defined as reintubations or the need for an alternate mode of oxygen support (per the treating physician's discretion), were similar between groups (21.0% for HFNC vs. 21.9% for NIV), although NIV masks caused more facial skin breakdown.

Researchers in three studies also compared HFNC with conventional oxygen after cardiac surgery. In the largest, 340 patients undergoing elective surgery that involved cardiopulmonary bypass were randomized to 45 liters per minute of HFNC or 2–4 liters per minute of conventional oxygen (58). Both interventions produced similar Sp_{O_2}/FI_{O_2} ratios on Postoperative Day 3. Fewer HFNC patients required escalation of respiratory support, although reintubations were rare in both groups, which likely contributed to the study's negative result. Researchers in another study randomized 155 obese patients (BMI, >30 kg/m^2) undergoing surgery who required cardiopulmonary bypass to 35–50 liters per minute of HFNC or 2–6 liters per minute of nasal cannula or face mask oxygenation for 8 hours after extubation (59). Oxygenation, dyspnea, and radiographic features of atelectasis were similar between the groups. In contrast, investigators reported better outcomes with HFNC in a study of 60 cardiac surgery patients with hypoxemic respiratory failure, defined as a supplemental oxygen requirement greater than 4 liters per minute by nasal cannula or greater than 6 liters per minute by face mask (60). Patients were randomized to 35 liters per minute of HFNC or oxygen by face mask. HFNC use resulted in fewer intubations than conventional oxygen (10% vs. 30%) and fewer desaturation episodes. On the basis of these results, HFNC is a reasonable alternative to NIV and conventional oxygen for treating hypoxemia and preventing reintubation after cardiothoracic surgery, particularly in high-risk patients intolerant of NIV.

Abdominal Surgery

HFNC was compared with conventional oxygen in 220 patients undergoing abdominal surgery who were at moderate or high risk of postoperative respiratory failure (61). Postoperative pulmonary risk was defined using the previously validated ARISCAT (Assess Respiratory Risk in Surgical Patients in Catalonia study) score (⩾26), which incorporates seven categories of comorbidities to predict postoperative pulmonary complications (62). Less than 10% of patients had preexisting lung disease, although almost one-third were current smokers. A majority of patients in the study were undergoing liver resection or pancreaticoduodenectomy and had known malignancies. HFNC set between 50 and 60 liters per minute and conventional oxygen had similar rates of hypoxemia 1 hour after extubation and pulmonary complications over 7 days. HFNC and conventional oxygen were delivered for an average of 15 and 16 hours, respectively. These results suggest that HFNC does not offer an

Table 3. Prospective trials of high-flow nasal cannula oxygenation in surgical patients

Study	Design/*N*	Patients	Comparison	Outcomes
Prevention of reintubation after cardiac surgery				
Corley and colleagues, 2015 (59)	RCT 155	BMI ⩾30 kg/m^2	HFNC 35–50 L/min vs. COT	No difference in $\mathrm{Pa_{O_2}}/\mathrm{FI_{O_2}}$ after 24 h No difference in atelectasis by Day 5
Parke and colleagues, 2013 (58)	RCT 340	Not stratified by reintubation risk	HFNC 45 L/min vs. usual care	No difference in $\mathrm{Sp_{O_2}}/\mathrm{FI_{O_2}}$ on Day 3 Fewer in HFNC group required escalation of respiratory support
Parke and colleagues, 2011 (60)	RCT 60	Surgical ICU Most were post–cardiac surgery	HFNC 35 L/min vs. COT	Lower NIV use with HFNC (10%) vs. COT (30%) Fewer desaturation events with HFNC
Stephán and colleagues, 2015 (57)	RCT 830	Previously failed extubation or high risk for reintubation	HFNC 50 L/min vs. NIV	No difference in reintubations or ICU mortality More skin breakdown with NIV
Prevention of reintubation after abdominal surgery				
Futier and colleagues, 2016 (61)	RCT 220	High risk for reintubation	HFNC 50–60 L/min vs. COT	No difference in reintubations, hypoxemia, or in-hospital mortality
Thoracic surgery				
Ansari and colleagues, 2016 (64)	RCT 59	Post–lung resection	HFNC 20–50 L/min vs. COT	HFNC reduced hospital LOS No difference in 6MWT on POD 2 Imbalance in baseline 6MWT may have influenced results
Yu and colleagues, 2017 (63)	RCT	Post-lobectomy High risk for reintubation	HFNC 35–60 L/min vs. COT	HFNC reduced intubations and hypoxemia

Definition of abbreviations: 6MWT = 6-minute walk test; BMI = body-mass index; COT = conventional low-flow oxygen therapy; $\mathrm{FI_{O_2}}$ = fraction of inspired oxygen; HFNC = high-flow nasal cannula; ICU = intensive care unit; LOS = length of stay; NIV = noninvasive positive pressure ventilation; $\mathrm{Pa_{O_2}}$ = arterial partial pressure of oxygen; POD = postoperative day; RCT = randomized controlled trial; $\mathrm{Sp_{O_2}}$ = oxygen saturation as measured by pulse oximetry.

additional benefit over conventional oxygen after abdominal surgery, albeit in a selected population undergoing hepatic and pancreatic interventions. The generalizability of these findings to other abdominal surgeries and patient populations remains to be determined.

Lung Resection

HFNC was compared with conventional oxygen after thoracoscopic lobectomy in patients at moderate or high risk for reintubation based on an ARISCAT score higher than 26 (63). One hundred ten patients were randomized postoperatively to 35–60 liters per minute of HFNC or low-flow oxygen by face mask or nasal cannula. Oxygen flow and $\mathrm{FI_{O_2}}$ were titrated to achieve oxygen saturation greater than 95%. HFNC reduced hypoxemia (12% vs. 29% incidence) and the need for NIV (4% vs. 17%). There were no reintubations in the HFNC group compared with five in the conventional oxygen group. Fewer respiratory complications may have accounted for modest cost savings seen with HFNC. In a separate study, 59 patients undergoing lung resection by video-assisted thoracoscopic surgery or thoracotomy were randomized to either 20–50 liters per minute of HFNC, adjusted for comfort and respiratory rate less than 16 breaths per minute, or 2–4 liters per minute of conventional oxygen (64). HFNC was associated with greater patient satisfaction and decreased length of stay. Overall, these studies suggest that HFNC reduces postoperative respiratory failure for patients at increased risk of pulmonary complications after surgical lung resection. This outcome may be especially relevant in this population, given the potential for surgical site air leak and delayed wound healing when noninvasive or invasive positive pressure ventilation is applied.

Preoxygenation and Apneic Oxygenation for Intubation

Preoxygenation is routinely used to prevent desaturation during endotracheal intubation, but preoxygenation practice varies widely and is often insufficient in critically ill patients (65). Furthermore, few modes provide oxygenation during intubation (apneic oxygenation), because masks (e.g., NIV full face masks or nonrebreather masks) must be removed before laryngoscopy. HFNC delivers oxygen during both phases of intubation.

In two studies, researchers compared preoxygenation with HFNC to NIV before laryngoscopy (Table 4). In a retrospective analysis of 52 patients, no episodes of severe desaturation ($\mathrm{Sp}_{\mathrm{O}_2}$, <70%) occurred in patients preoxygenated with HFNC compared with five events in patients preoxygenated with NIV (66). Similarly, in the randomized, double-blind OPTINIV (Noninvasive Ventilation Combined with High-Flow Nasal Cannula Oxygen for Preoxygenation of Hypoxemic ICU Patients) trial, preoxygenation with 60 liters per minute of HFNC combined with NIV (inspiratory pressure, 10 cm H_2O; expiratory pressure, 5 cm H_2O; 100% $\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$) resulted in better oxygenation and less frequent episodes of severe desaturation ($\mathrm{Sp}_{\mathrm{O}_2}$, <80%) during intubation than NIV alone (67).

Preoxygenation with HFNC delivered at 60 liters per minute was compared with 15 liters per minute of face mask oxygen in medical patients with acute respiratory failure (68). Patients on HFNC also received apneic oxygenation throughout laryngoscopy. The researchers in that study found no difference in the frequency of desaturation during intubation, although nearly one-fourth of patients in both groups developed oxygen saturation less than 80% during laryngoscopy. HFNC delivered at 50 liters per minute was also compared with bag mask ventilation in 40 surgical patients undergoing intubation. HFNC and bag mask ventilation were equally effective for preoxygenation and resulted in the same rate of desaturation below 80% (five per group) (69).

Apneic oxygenation with HFNC was evaluated in critically ill medical patients. Semler and colleagues randomized 150 patients to 15 liters per minute of HFNC versus no supplemental oxygen during intubation (70). The groups had similar rates of hypoxemia, although the low flow rate chosen for this study likely limited the efficacy of HFNC. In contrast, in a controlled before-after study, researchers compared apneic oxygenation with 60 liters per minute of HFNC with the combination of preoxygenation with a 15 liters per minute face mask followed by apneic oxygenation with a 6 liters per minute nasal cannula. Fewer desaturations occurred with HFNC. Only one patient had saturation less than 80% with HFNC, compared with seven patients in the control group (71).

Given substantial study heterogeneity, the generalizability of these results is unclear. HFNC appears to be a reasonable option for preoxygenation. It is not clearly superior to other common modes, but it has the added advantage of providing apneic oxygenation during laryngoscopy.

High-Flow Nasal Cannula Use during Bronchoscopy

Respiratory drive and mechanics are altered during bronchoscopy owing to procedural sedation and partial occlusion of the airway by the bronchoscope (72). As a result, oxygen saturation may fall below 90% despite oxygen supplementation (73). NIV can prevent hypoxemia during bronchoscopy (74), but mask intolerance and difficulty in manipulating the scope through the mask limits its appeal. HFNC permits oral passage of the bronchoscope and may improve oxygenation during the procedure. To test this, Lucangelo and

Table 4. Prospective trials of high-flow nasal cannula oxygenation for intubation and bronchoscopy

Study	Design/*N*	Patients	Comparison	Outcomes
Preoxygenation and apneic oxygenation for intubation				
Jaber and colleagues, 2016 (67)	RCT 49	RR ⩾30 breaths/min, $\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$ >50% $\mathrm{Pa}_{\mathrm{O}_2}/\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$ <300 requiring MV	Preoxygenation with HFNC 60 L/min + NIV vs. NIV alone	HFNC + NIV combination improved oxygenation vs. NIV alone
Miguel-Montanes, and colleagues, 2015 (71)	Before-after 101	All patients requiring MV	Before: NRB After: HFNC 60 L/min	HFNC reduced severe hypoxemia ($\mathrm{Sp}_{\mathrm{O}_2}$ <80%)
Semler and colleagues, 2016 (70)	RCT 150	All patients requiring MV	HFNC 15 L/min during laryngoscopy vs. no oxygen	No difference in hypoxemia
Simon and colleagues, 2016 (69)	RCT 40	$\mathrm{Pa}_{\mathrm{O}_2}/\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$ <300 requiring MV	HFNC 50 L/min before/during laryngoscopy vs. bag mask before	No difference in hypoxemia
Vourc'h and colleagues, 2015 (68)	RCT 124	RR ⩾30 breaths/min, $\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$ ⩾50%, $\mathrm{Pa}_{\mathrm{O}_2}/\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$ <300 requiring MV	HFNC 60 L/min before/during laryngoscopy vs. face mask before	No difference in hypoxemia No difference in adverse events
Bronchoscopy				
Lucangelo and colleagues, 2012 (75)	RCT 45	Diagnostic bronchoscopy No respiratory or cardiac failure	HFNC 40 L/min, HFNC 60 L/min, or Venturi mask 40 L/min	60 L/min HFNC improved hypoxemia and $\mathrm{Pa}_{\mathrm{O}_2}/\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$ ratio better than 40 L/min HFNC and Venturi mask
Simon and colleagues, 2014 (76)	RCT 40	Diagnostic bronchoscopy $\mathrm{Pa}_{\mathrm{O}_2}/\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$ <300	HFNC 50 L/min vs. NIV	Similar oxygenation during procedure One HFNC, three NIV required intubation within 24 h Approximately three-fourths of patients were on NIV or HFNC at baseline

Definition of abbreviations: $\mathrm{F}_{\mathrm{I}_{\mathrm{O}_2}}$ = fraction of inspired oxygen; HFNC = high-flow nasal cannula; MV = mechanical ventilation; NIV = noninvasive positive pressure ventilation; NRB = nonrebreather mask; $\mathrm{Pa}_{\mathrm{O}_2}$ = arterial partial pressure of oxygen; RCT = randomized controlled trial; RR = respiratory rate; $\mathrm{Sp}_{\mathrm{O}_2}$ = oxygen saturation as measured by pulse oximetry.

colleagues prospectively randomized 45 adults without respiratory or cardiac failure who were undergoing bronchoscopy to HFNC set at 40 liters per minute with 50% $F_{I_{O_2}}$, HFNC set at 60 liters per minute with 50% $F_{I_{O_2}}$, or Venturi mask with 50% $F_{I_{O_2}}$ (75). Patients were sedated with midazolam for the duration of the procedure (average, ∼15 min). HFNC with 60 liters per minute flow produced marginally higher oxygen saturation at the end of the procedure than HFNC at 40 liters per minute or Venturi mask (98% compared with 94% and 92%, respectively). Subjects reported similar levels of comfort with all modes. Thus, HFNC and the Venturi mask are both reasonable options during routine bronchoscopy in patients without existing respiratory failure.

The more challenging clinical scenario, however, is performing bronchoscopy in patients with preexisting respiratory failure. Can HFNC prevent complications and facilitate bronchoscopy in this population? To evaluate this question, Simon and colleagues randomized patients with respiratory failure, defined as a $Pa_{O_2}/F_{I_{O_2}}$ ratio less than 300, to 50 liters per minute of HFNC or NIV (inspiratory pressure, 15–20 cm H_2O; expiratory pressure, 3–10 cm H_2O) throughout bronchoscopy (76). Ventilatory support with either HFNC or NIV was required in almost 75% of patients before randomization. Patients were sedated with propofol throughout the procedure (∼5 min in both groups). HFNC and NIV produced similar nadirs in oxygenation during the procedure (92 ± 7% and 95 ± 5%, respectively). One patient in the HFNC group and three patients in the NIV group required intubation within 24 hours of the procedure. Similar results were reported in a prospective, observational study of 30 patients undergoing bronchoscopy with hypoxemia, defined as a supplemental oxygen requirement of greater than 6 liters per minute (77). All patients received 50–60 liters per minute of HFNC with 80 to 100% $F_{I_{O_2}}$. Five patients required escalation of respiratory support within 24 hours of the procedure (two intubations, three NIV), although none required intubation during or immediately after the procedure. For most patients, dyspnea scores returned to baseline 1 hour after the procedure. These studies suggest that HFNC can provide support for hypoxemic patients undergoing bronchoscopy and should be considered when evaluating procedural risks and benefits in high-risk populations.

Future Research Directions

Despite significant advances in our understanding of the effectiveness of HFNC, many areas of uncertainty remain that should guide future study design. In the current literature, wide variations in inclusion criteria, device flow rates, $F_{I_{O_2}}$ settings, and durations of therapy make comparisons between studies challenging. It remains unknown whether the benefits of HFNC require flows above a specific threshold. Studies often use surrogate endpoints such as $Pa_{O_2}/F_{I_{O_2}}$, which may not reflect clinically relevant outcomes such as mortality and intubations. In addition, studies have relied on a variety of supplemental oxygen modes in control groups, highlighting the lack of a clinical "gold standard" against which to compare HFNC. Clinicians would benefit from studies that identify early predictors of HFNC success, as well as from an improved understanding of signs that constitute therapy failure. Methods of HFNC weaning also require examination. Finally, the effects of HFNC on oxygenation, work of breathing, and mortality have not been explored sufficiently for many diagnoses that either were excluded from earlier trials (e.g., exacerbations of chronic obstructive pulmonary disease) or were not addressed in a robust, prospective manner (e.g., heart failure) (78, 79). Future studies should continue to define optimal device settings and assess meaningful outcomes in well-characterized patient populations to aid clinical decision making. ■

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