Year in Review 2019: High-Flow Nasal Cannula Oxygen Therapy for Adult Subjects

Jie Li, Guoqiang Jing, and J Brady Scott

Many high-quality clinical trials and meta-analyses on the utilization of high-flow nasal cannula for adult patients have been published in the last 2 years. This review summarizes the recent clinical evidence, with the aim to provide the currently available evidence regarding the utilization of high-flow nasal cannula for the adult patient. *Key words: high-flow nasal cannula; oxygen therapy; acute respiratory failure; chronic obstructive pulmonary disease; noninvasive ventilation.* [Respir Care 2020;65(4):545–557. © 2020 Daedalus Enterprises]

Introduction

High-flow nasal cannula (HFNC) is a relatively new modality of oxygen therapy that delivers warmed, humidified gas at a flow exceeding a patient's inspiratory flow demand.[1] Since 2018, 20 randomized controlled trials (RCTs) [2-21] and 10 meta-analyses[22-31] (Table 1) have been published on HFNC for adult subjects with different clinical conditions. The prediction of HFNC success and aerosol delivery via HFNC have emerged as topics of considerable focus during

Dr Li and Mr Scott are affiliated with the Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University Medical Center, Chicago, Illinois. Mr Jing is affiliated with the Department of Pulmonary and Critical Care Medicine, Binzhou Medical University Hospital, Binzhou, Shandong, China.

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Correspondence: Jie Li PhD RRT RRT-ACCS RRT-NPS, 1620 W Harrison St, Tower LL1202, Chicago, IL 60612. E-mail: jie_li@rush.edu.

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this time. Pertinent findings from these recent publications are discussed in this review, and recommendations are made based on the current evidence (Table 2).

HFNC Utilization in Various Clinical Conditions

Acute Hypoxemic Respiratory Failure

A known advantage of HFNC is that gas delivered from the device meets or exceeds patient inspiratory flow demand and provides a constant F_{IO_2}. As a result, HFNC has been utilized to treat acute hypoxemic respiratory failure for the past decade. Between 2016 and 2018, 4 meta-analyses have reported its superiority over conventional oxygen therapy and its noninferiority to noninvasive ventilation (NIV) for the improvement of oxygenation and the avoidance of intubation in hypoxemic subjects.[28,32-34] It should be noted, however, that the number of subjects included in the meta-analyses was < 1,000. In late 2018, Azoulay et al[18] published an RCT that included 776 immunocompromised subjects with acute hypoxemic respiratory failure. Contrary to the findings from the 4 meta-analyses,[28,32-34] these investigators did not find a significant difference in intubation and mortality between the HFNC and O_2 therapy groups.[18] The large number of the subjects in this study, as well as the contradictory findings, triggered updates to the evidence pertaining to HFNC use in acute hypoxemic respiratory failure. In 2019, Rochwerg et al[22] published a systematic review and meta-analysis that included 9 RCTs with 2,093 subjects. They reported that the risk of intubation was found to be lower in subjects treated with HFNC compared to subjects treated with O_2 therapy (relative risk 0.85, 95% CI 0.74–0.99), even though there was no difference between hospital mortality, ICU length of stay, and hospital length of stay.[22] In the meta-analysis by Rochwerg et al,[22] studies on the use of HFNC for the treatment of postextubation respiratory failure were excluded. Shen et al[29] deemed that the exclusion was unnecessary and might cause selection bias. An update on the meta-analysis included 11 RCTs in which the authors noted that the subjects' baseline was an essential factor affecting heterogeneity. In their subgroup analysis that separated subjects on the basis of $P_{aO_2}/F_{IO_2} > 200$ mm Hg or ≤ 200 mm Hg, they reported that subjects with $P_{aO_2}/F_{IO_2} > 200$ mm Hg, particularly postextubation subjects, had the greatest benefit from HFNC. Additionally, of the 9 RCTs included in the meta-analysis by Rochwerg et al,[22] 4 were completed in emergency department. Tinelli et al[30] analyzed these 4 RCTs and observed no significant benefits of HFNC over O_2 therapy in subjects with acute hypoxemic respiratory failure in the emergency department. Therefore, future studies are needed to clarify the role of HFNC in subjects with different severity, pathophysiology, and treatment location.

Immunocompromised Subjects With Acute Respiratory Failure. The goals of therapy when treating an immunocompromised patient with acute hypoxemic respiratory failure are to correct hypoxemia and avoid intubation.[31] HFNC is a reasonable solution for these patients because it is well-tolerated and noninvasive. After the study by Azoulay et al[18] was published, several systematic reviews and meta-analyses were completed on the use of HFNC for immunocompromised subjects with acute respiratory failure.[23,24,31] In the meta-analysis by Cortegiani et al,[23] they included one retrospective study as well as post hoc analyses from 2 RCTs, in addition to the study by Azoulay et al.[18] Compared to O_2 therapy, HFNC reduced the risk of intubation in immunocompromised subjects in the ICU with acute hypoxemic respiratory failure ($n = 1,052$ subjects, odds ratio 0.74, 95% CI 0.55– 0.98, $P = .03$), but HFNC did not reduce the risk of ICU mortality or 28-d mortality. In the meta-analysis published by Kang et al,[24] even though they included the 4 studies excluded by Cortegiani et al,[23] their findings supported the superiority of HFNC over O_2 therapy to reduce intubation rate. It is noted that they did not find any significant differences between HFNC and NIV, which was in agreement with the recent pairwise and network meta-analysis.[31] Despite these findings, it should be emphasized that there have been no published RCTs that directly compare HFNC and NIV in immunocompromised patients, and future high-quality RCTs are warranted.

Available evidence suggests that, compared to O_2 therapy, HFNC can reduce the risk of intubation for patients with acute hypoxemic respiratory failure, including those who are immunocompromised. However, evidence has not shown a benefit for length of hospital stay or mortality. The benefit of HFNC is more evident for patients with mild hypoxemia ($P_{aO_2}/F_{IO_2} > 200$ mm Hg). The evidence that compares HFNC versus NIV as the initial respiratory support for patients with acute hypoxemic respiratory failure is limited, particularly for immunocompromised patients. Future studies that focus on subjects with $P_{aO_2}/F_{IO_2} \leq 200$ mm Hg and comparisons of HFNC and NIV are needed.

Postextubation Subjects

Planned Extubation and Postsurgery Patients: HFNC Versus O_2 Therapy. At the time of extubation, patients are often placed on room air or O_2 therapy, if needed. In 2010, Tiruvoipati et al[35] initiated the first RCT comparing 1 h of HFNC at 30 L/min to face mask O_2 therapy for subjects extubated in the ICU. No differences in gas exchange, breathing frequency, or postextubation respiratory failure were found, although the investigators did note a trend toward improved comfort with HFNC.[35] Since this RCT was published, others sought to better understand the role of postextubation HFNC. Zhu et al[25] published a meta-analysis that compared the use of HFNC to O_2 therapy for

Table 1. Evidence for HFNC Use in Various Clinical Conditions

Indication	Study	Comparison	Included RCTs, *n* (*N* subjects)	Findings			
				HFNC Risk for Intubation/ Re-intubation	HFNC Risk for Escalation of Therapy	Mortality	Other
Acute hypoxemic respiratory failure	Rochwerg et al[22]	HFNC vs O_2 therapy	9 (2,093)	0.85 (0.74–0.99)	0.71 (0.51–0.98)	0.94 (0.67–1.31)	No difference in ICU or hospital length of stay, subject-reported comfort or dyspnea
Immunocompromised subjects with acute respiratory failure	Kang et al[24]	HFNC vs O_2 therapy	4 (1,112)	0.87 (0.75–1.00)	Unreported	1.0 (0.82–1.23)	No difference in ICU-acquired infections compared with O_2 therapy
	Cortegiani et al[23]	HFNC vs O_2 therapy	4 (1,052)	0.74 (0.55–0.98)*	Unreported	0.80 (0.44–1.45)*	
Subjects after planned extubation	Zhu et al[25]	HFNC vs O_2 therapy	10 (1,708)	No significant differences	0.61 (0.41–0.92)	No significant differences	HFNC significantly reduced breathing frequency and increased P_{aO_2}; no difference in ICU and hospital length of stay, comfort score, P_{aCO_2}, or adverse events
Postoperative adult surgical subjects	Lu et al[26]	HFNC vs O_2 therapy	10 (1,327)	0.38 (0.23–0.61)	0.43 (0.26–0.73)	0.45 (0.16–1.29)	No difference in the incidence of postoperative pulmonary complications
Preoxygenation before intubation in adult subjects with acute hypoxemic respiratory failure	Fong et al[27]	HFNC vs NIV	7 (959)	Not studied	Not studied	No significant differences	NIV had fewer desaturations than HFNC (mean difference 3.58, 95% CI 0.59– 6.57). Both NIV (OR 0.43, 95% CI 0.21–0.87) and HFNC (OR 0.49, 95% CI 0.28–0.88) had a lower risk of intubation-related complications than O_2 therapy.

Findings are presented as relative risk (95% CI) unless otherwise noted.
*These findings are presented as odds ratio (95% CI).
HFNC = high-flow nasal cannula
O_2 therapy = conventional oxygen therapy
NIV = noninvasive ventilation
RR = risk ratio
OR = odds ratio

Table 2. Recommendations on the Utilization of HFNC for Different Diseases

Indication	Take Home Messages
Acute hypoxemic respiratory failure	Compared to O_2 therapy, HFNC reduces the risk of intubation, particularly in the patients with mild hypoxemia ($P_{aO_2}/F_{IO_2} > 200$ mm Hg)
Immunocompromised patients with acute respiratory failure	Compared to O_2 therapy, HFNC reduces the risk of intubation
Postextubation	
Planned extubation (low-risk patients): HFNC vs O_2 therapy	Compared to O_2 therapy, HFNC reduces the risk of developing postextubation failure but does not decrease re-intubation rate
Postsurgery patients: HFNC vs O_2 therapy	Controversial
High-risk patients: HFNC vs NIV	Compared to the use of HFNC or NIV alone, use of NIV for 48 h and HFNC use in the NIV break might reduce re-intubation rate
Preoxygenation before intubation: HFNC vs NIV	HFNC is superior to O_2 therapy (but inferior to NIV) in avoiding intubation-related complications. Using a resuscitator bag or critical care ventilator to preoxygenate patients before intubation might be more cost-effective
Breathing support during endoscopy	Effectiveness of preventing hypoxia during endoscopy: NIV > HFNC > O_2 therapy
COPD	
Stable COPD	Long-term (≥ 6 wk) use of HFNC can improve CO_2 retention for patients with stable hypercapnic COPD, improve quality of life, and reduce COPD exacerbations
During exercise	HFNC may improve exercise endurance time if S_{pO_2} is maintained > 90%
COPD exacerbation	HFNC may be considered as an alternative to NIV in mild to moderate COPD, but more robust evidence is warranted
Postextubation	HFNC may be considered as an alternative to NIV to facilitate weaning patients with COPD and stable hypercapnia from invasive ventilation, although more robust evidence is warranted

HFNC = high-flow nasal cannula
O_2 therapy = conventional oxygen therapy
NIV = noninvasive ventilation

subjects after planned extubation. Seven RCTs and 3 crossover RCTs were included, with 1,708 subjects enrolled. Five of the RCTs indicated that HFNC reduced the risk of the development of respiratory failure after extubation (relative risk 0.61, 95% CI 0.41–0.92, $P = .02$). However, HFNC did not reduce the risk of re-intubation in the 7 RCTs. It is important to note that the heterogeneity of the studies included in the meta-analysis was of concern. As such, the authors performed subgroup analyses on the HFNC duration (≥ 24 h vs < 24 h), gas flow (≥ 40 L/min vs < 40 L/min), disease severity, and hypercapnia versus non-hypercapnia; they found no significant interaction between HFNC versus O_2 therapy.[25] Also, only about one third of the subjects with postextubation respiratory failure in either group were re-intubated (HFNC: 48 of 136 per 1,000 subjects; O_2 therapy: 82 of 219 per 1,000 subjects).[25] This may imply the importance of the timely escalation of therapy, such as switching from O_2 therapy to HFNC/NIV or from HFNC to NIV in an effort to avoid re-intubation.

After this meta-analysis, 4 new RCTs on postsurgery subjects were published.[2,4,8,17] For post-cardiac surgery subjects, compared to O_2 therapy, the prophylactic use of HFNC after extubation was reported to improve oxygenation and reduce the need for NIV.[2] HFNC was also reported to reduce the ICU readmission and hospital length of stay in this population.[17] For obese subjects who underwent bariatric surgery, compared to O_2 therapy, the use of HFNC immediately after extubation significantly improved oxygenation within 3 h and reduced pulmonary complications during hospitalization.[4] These results are contradictory to previous studies in subjects with abdominal surgery[36] and obese subjects with cardiac surgery,[37] which did not indicate any significant difference between HFNC and O_2 therapy on all outcomes. For subjects who underwent lung resection, there was no significant difference of postoperative hypoxemia, respiratory failure, or pulmonary complications between HFNC and air-entrainment mask groups.[8] These findings are also contradictory to the results of a study that compared HFNC with O_2 therapy for subjects after thoracoscopic lobectomy, in which HFNC was shown to reduce the risk of re-intubation.[38] Future studies on the use of HFNC for postsurgical subjects with considerations regarding specific type of surgery and outcomes are needed.

High-Risk Patients: HFNC Versus NIV. In 2016, Hernández et al[39] published the first multicenter RCT to compare the use of HFNC versus NIV in subjects who had one or more high risk factors for extubation failure. No significant differences of re-intubation rates were noted between HFNC

Table 3. Comparisons of 2 RCTs on Postextubation Subjects With High Risk for Extubation Failure

	Hernández et al[39]			Thille et al[11]		
	HFNC	NIV	*P*	HFNC	NIV+HFNC	*P*
Subjects, *n*	290	314	ND	302	339	ND
Underlying chronic lung disease, *n* (%)	54 (18.6)	70 (22.3)	ND	87 (29)	126 (37)	ND
Duration of mechanical ventilation before extubation, h, median (IQR)	4 (2–9)	4 (2–8)	ND	5 (3–9)	6 (3–11)	ND
Respiratory primary failure, *n* (%)	98 (33.8)	121 (38.5)	ND	158 (52)	167 (49)	ND
Settings	50 ± 5 L/min	To achieve V_T = 8 mL/kg, f = 25 breaths/min	ND	50 ± 5 L/min	Pressure support 7.8 ± 2.5 cm H_2O PEEP 5.3 ± 1.1 cm H_2O	ND
Length of utilization, h, median (IQR)	24	14 (8–23) in the first 24 h	ND	42 ± 11 h in the first 48 h	NIV 22 ± 9 h in the first 48 h	ND
Postextubation respiratory failure, *n* (%)	78 (26.9)	125 (39.8)	< .001	88 (29)	70 (21)	.01
All-cause re-intubation within 72 h, *n* (%)	66 (22.8)	60 (19.1)	.27	47 (16)	30 (9)	.009
Re-intubation within 24 h, *n* (%)	30 (10.3)	35 (11.1)	.75	26 (8.6)	18 (5.3)	.10
Re-intubation within 48 h, *n* (%)	56 (19.3)	45 (14.3)	.10	36 (12)	24 (7)	.04
Respiratory-caused re-intubation, *n* (%)	49 (16.9)	50 (15.9)	.75	46 (15)	42 (12)	.30
Time to re-intubation, h, median (IQR)	26.5 (14–39)	21.5 (10–47)	ND	39 (12–67)	33 (7–81)	.76

RCT = randomized controlled trial
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation
ND = no data
IQR = interquartile range
V_T = tidal volume
f = breathing frequency

and NIV, however, the incidence of postextubation failure was higher in the NIV group (39.8% vs 26.9%, $P < .001$). In contrast, Thille et al[11] completed a multicenter RCT on a similar subject population in 2019 and reported a lower incidence of postextubation respiratory failure (21% vs 29%, $P = .01$) and re-intubation rate (9% vs 16%, $P = .009$) in the NIV group compared to the HFNC group. The opposing results from these 2 similar studies might be due to the way NIV was utilized (Table 3). In the study by Hernández et al,[39] the actual duration of NIV use was only 14 (8–23) h out of 24 h. In the study by Thille et al,[11] NIV was used for 22 ± 9 h out of 48 h; in addition, HFNC was used during breaks from NIV, whereas Hernández et al[39] utilized O_2 therapy. Spoletini et al[16] reported that the use of HFNC instead of O_2 therapy during NIV breaks improved subject comfort and reduced the incidence of dyspnea. This might explain why the incidence of postextubation respiratory failure in NIV group was higher in the study by Hernández et al[39] than the study by Thille et al[11] (39.8% vs 21%). Admittedly, it is difficult to tell which factor (ie, extended use of NIV or HFNC use during NIV break), if any, played a key role in the outcome. Additionally, when comparing the 2 studies, it is important to note the duration of HFNC use. With similar flow settings (50 ± 5 L/min), the re-intubation rate in both studies was similar within 24 h postextubation in the HFNC groups (10.3% vs 8.6%). However, HFNC therapy was withdrawn after 24 h in the study by Hernández et al,[39] and the re-intubation rate was nearly doubled at 48 h in HFNC group. In contrast, there was only a slight increase in the re-intubation rate in the Thille et al[11] study, which continued the use of HFNC for 48 h.[1]

In all, for patients who are to be routinely extubated or at low risk of re-intubation, HFNC may reduce the risk of developing postextubation respiratory failure compared to O_2 therapy. However, this does not imply that clinicians need to use HFNC for all patients who are to be extubated because the incidence of postextubation respiratory failure and re-intubation is already low in this population. The prophylactic use of HFNC in patients at low-risk for extubation failure may be a significant waste of resources. The use of HFNC for postsurgical patients remains controversial. Future studies in this population are needed, with an emphasis on type of surgery and specific

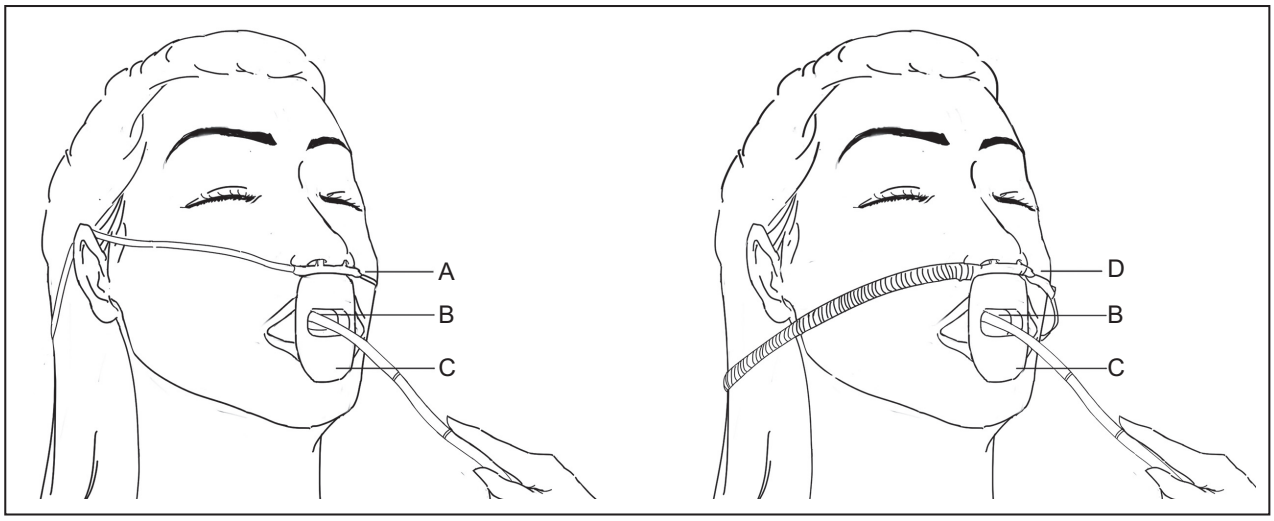

Fig. 1. Using high-flow nasal cannula (HFNC) and conventional nasal cannula during endoscopy examination: (A) conventional nasal cannula; (B) endoscopy; (C) bite block; (D) HFNC. Modified from Reference 14.

outcomes (eg, postoperative hypoxemia, prevention of respiratory failure, development of pulmonary complications). Compared to the prophylactic use of HFNC for all patients, it might be wise to identify those patients who are at risk for developing respiratory failure after extubation using O_2 therapy. Identification of the appropriate time to escalate treatments, such as the switch from O_2 therapy to HFNC/NIV or switch from HFNC to NIV to avoid re-intubation is also needed. Similarly, for patients who are at high risk for re-intubation after extubation, the use of NIV for all patients is also unnecessary. Future studies on identifying the correct patients and the correct timing for postextubation NIV are still warranted. Finally, the duration of HFNC/NIV use and the use of HFNC during breaks from NIV may play a vital role for those patients at risk for extubation failure, but more studies are needed.

Preoxygenation Before Intubation: HFNC Versus NIV

A recent meta-analysis demonstrated that preoxygenation with HFNC prior to intubation in adult subjects with hypoxemia reduced the risk of intubation-related complications compared to O_2 therapy. However, when compared to NIV, subjects treated with HFNC had more desaturation (Table 1).[27] Interestingly, all 7 of the RCTs using HFNC to preoxygenate subjects before intubation were completed in Europe, with 6 of them in France. It appears that the clinicians in Europe, particularly in France, are more familiar with the process of using HFNC to preoxygenate patients prior to intubation compared to clinicians in other areas of the world. In a recent nationwide survey among French ICU physicians, unsurprisingly, 84% of them agreed that use of HFNC to preoxygenate patients before intubation was a good use of the modality.[40] Clinically, the duration of preparing acute hypoxemic patients for intubation is short and usually takes no more than 10 min. If patients are not already being treated with HFNC therapy, the time to set up the device may be unnecessary, especially considering the financial cost. There are several other measures available at the bedside, such as a manual resuscitator (with a PEEP valve) or a critical care ventilator (with mask), which could maintain higher mean airway pressure and better ventilation compared to HFNC. The manual resuscitator would already be needed for patients who are heavily sedated or paralyzed before and after intubation. Intubation-related complications and cost-effectiveness studies are needed in the future to compare the use of HFNC versus manual resuscitator/ventilator to preoxygenate patients for intubation.

Breathing Support During Endoscopy

There has been an increasing interest in the use of HFNC for oxygen therapy during endoscopy recently (Fig. 1), with 4 RCTs published on this topic in 2019. In total, there have been 6 RCTs completed, with 3 during bronchoscopy and 3 during esophagogastroduodenoscopy (Table 4).[7,10,13-15,41] HFNC has been reported to be less effective than NIV[10,13,41] but to be superior to O_2 therapy[7,14,15] in maintaining oxygenation during endoscopic examination. In the 3 RCTs with nonhypoxemic subjects, it should be noted that the HFNC F_{IO_2} was set at 1.0 with flow at 30–60 L/min. This is compared to oxygen flow at 2–10 L/min using a regular nasal cannula.[7,14,15] Considering the higher oxygen flows utilized during HFNC, the lower incidence of hypoxia in HFNC group was expected. In contrast, Riccio et al[13] reported that, if the F_{IO_2} for subjects in HFNC group was set at 0.36–0.4, similar to the F_{IO_2} used by the subjects in the control group (nasal cannula 4

Table 4. RCTs Comparing HFNC and O_2 Therapy or NIV During Endoscopy

Study Characteristics	Simon et al[41]	Douglas et al[15]	Saksitthichok et al[10]	Lin et al[7]	Teng et al[14]	Riccio et al[13]
Subjects, *N*	40	60	51	1,994	101	59
Country	Germany	Australia	Thailand	China	Taiwan	United States
Procedure	Bronchoscopy	Bronchoscopy	Bronchoscopy	Gastroscopy	Esophagogastroduodenoscopy	Colonoscopy
Indication	Hypoxemic respiratory failure	Adults planned for conscious sedation for endobronchial ultrasound	Hypoxemic patients	Outpatients undergoing routine gastroscopy with propofol sedation	Patients need sedative	Obese
Comparison	HFNC at 50 L/min vs NIV; F_{IO_2} = 1.0 for both devices	HFNC at 50 L/min; F_{IO_2} 1.0 vs nasal cannula at 10 L/min	HFNC at 40 L/min; F_{IO_2} 0.6 vs NIV	HFNC at 60 L/min; F_{IO_2} 1.0 vs nasal cannula at 2 L/min	HFNC at 30 L/min; F_{IO_2} 1.0 vs nasal cannula at 5 L/min	HFNC at 60 L/min; F_{IO_2} 0.36–0.4 vs nasal cannula at 4 L/min
Incidence of hypoxia ($S_{pO_2} \leq 90\%$)	Oxygenation was lower with HFNC than NIV	13.3 vs 33.3% ($P = .07$)	34.6 vs 12.0% ($P = .057$)	0 vs 8.4% ($P < .001$)	2 vs 20% ($P = .004$)	39.3% vs 45.2% ($P = .79$)

RCT = randomized, controlled trial
HFNC = high-flow nasal cannula
NIV = noninvasive ventilation

L/min), the incidence of hypoxia was similar in both HFNC and regular nasal cannula groups during colonoscopy despite an HFNC flow of 60 L/min (39.3% vs 45.2%, $P = .79$). This finding, with the aforementioned studies,[7,14,15] provides evidence that HFNC can reduce the incidence of hypoxia when a high F_{IO_2} (1.0) and high flow are used together. In the largest study ($N = 1{,}994$ subjects), only 8.4% of subjects undergoing gastroscopy experienced hypoxia in the nasal cannula group with a flow of 2 L/min oxygen.[7] Considering the cost-effectiveness of using HFNC during endoscopy, it may be unnecessary to use HFNC for all patients, and it might be worthwhile to reserve its use for high-risk patients, such as those with hypoxemia or hypercapnia.[10,41] Future studies are needed to identify the patients who benefit from HFNC during endoscopy.

COPD

In the past, HFNC was thought to improve oxygenation whereas NIV was thought to improve ventilation and oxygenation. Because of this, NIV has been more commonly used to treat patients with COPD due to the need for ventilatory support. Recently, physiologic studies have reported that HFNC can reduce CO_2 due to the effects of washing out dead space, prompting an increased interest in the use of HFNC for COPD patients.[42–45] In 2019, Pisani et al[46] published a systematic review on the utilization of HFNC for COPD exacerbation. HFNC has also been evaluated for postextubation support of subjects with COPD, for long-term domiciliary use, and for facilitating exercise for subjects with stable COPD.

COPD Exacerbation. There has been only 1 RCT published on the utilization of HFNC during COPD exacerbations.[47] The quality of the study is of concern, due to the fact that 19% of subjects dropped out and the ambiguity of the study design. In total, 88 subjects were enrolled for final analysis, and no significant difference was noted between the HFNC and NIV groups regarding intubation rate and 30-d hospital mortality. Also, the arterial blood gases after 6 and 24 h of utilization were not significantly different between the 2 groups.[47] This finding was similar to a recent observational cohort study comparing HFNC with NIV for COPD with acute to moderate hypercapnic respiratory failure. In that study, the authors reported a similar incidence of treatment failure between the 2 groups.[48] They also reported fewer incidences of skin breakdown and nursing interventions in HFNC group (Table 5).[48] In a crossover physiological study, Longhini et al[49] enrolled 30 subjects with COPD exacerbation who had used NIV for > 24 h. Five 30-min trials were designed; HFNC and O_2 therapy were randomly assigned in the second and fourth trials, and NIV was utilized in the other 3 trials. Diaphragm thickening fraction increased significantly during the O_2 therapy

Table 5. Clinical Studies Comparing HFNC and NIV for COPD Exacerbation or Postextubation

Study	Study Type	Subjects, *N*	Indication	Treatment	HFNC	Control	Intubation/ Re-intubation	Gas Exchange	Other Results
Pilcher et al[45]	Cross-over RCT	24	COPD exacerbation	Initial breathing support	35 L/min	O_2 therapy	NA	HFNC reduced P_{tcCO_2} more than O_2 therapy within 30 min	f reduction at 30 mins was not significantly different between HFNC and O_2 therapy
Lee et al[47]	Prospective observational study	88	COPD exacerbation with moderate hypercapnic acute respiratory failure	Initial breathing support	45–60 L/min	NIV	25.0% vs 27.3%, $P = .85$	No significant difference was noted between HFNC and NIV at 6 h and 24 h	30-d mortality 15.9% vs 18.2% ($P = .85$)
Longhini et al[49]	Physiological cross-over trial	30	COPD with hypercapnic acute respiratory failure receiving NIV > 24 h	Initial breathing support	50 L/min	NIV and O_2 therapy	NA	P_{aCO_2} and pH were not different among devices, but P_{aO_2} was greater with NIV	Diaphragm thickening fraction with HFNC was similar to NIV, and lower than O_2 therapy
Sun et al[48]	Observational cohort study	82	COPD with moderate hypercapnic acute respiratory failure	Initial breathing support	50 (40–50) L/min	NIV	20.5% vs 21.4%	No significant difference was noted between HFNC and NIV at 24 h	28-d mortality: 15.4% vs 14% ($P = .82$)
Thille et al[11]	Subgroup analysis from a large RCT	111	Hypercapnic respiratory failure	Postextubation	50 ± 5 L/min	NIV+HFNC	21% vs 8%, $P = .049$	NA	ICU mortality: 10% vs 3% ($P = .12$); postextubation respiratory failure at day 7: 50% vs 22% ($P = .002$)
Jing et al[6]	RCT	42	COPD with persistent hypercapnia	Postextubation	52.4 ± 6.3 L/min	NIV	9.1% vs 5%, $P = .93$	pH was lower with NIV than HFNC at 3 and 24 h	Fewer subjects with HFNC needed bronchoscopy for secretion management within 48 h after extubation: 2 of 22 vs 9 of 20 ($P = .008$)

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NIV = noninvasive ventilation
RCT = randomized, controlled trial
f = breathing frequency

trial, whereas it remained unchanged during the HFNC trial.[49] This promising finding may support HFNC as alternative to NIV in mild to moderate COPD patients, although more high-quality studies are warranted before making conclusion. Cortegiani et al[50] are currently conducting an RCT to compare the use of HFNC and NIV for exacerbations of COPD with mild to moderate hypercapnic acute respiratory failure. This trial may provide important insight in the role of HFNC for mild to moderate exacerbations of COPD.

Postextubation. In the large multi-center RCT by Thille et al[11] that compared HFNC with NIV+HFNC, 111 of the 641 subjects had hypercapnic respiratory failure, and the cumulative re-intubation rate at day 7 was higher in the group treated by HFNC alone (Table 5). It should be emphasized that HFNC therapy was only utilized for 48 h, and the cumulative re-intubation rate at 48 h was not significantly different between the 2 groups (8% vs 3%, $P = .23$).[11] If HFNC was used for longer periods of time, it is plausible that the re-intubation rate at day 7 would have been different. Jing et al[6] published an RCT that enrolled 42 subjects with COPD who had hypercapnia at extubation. The authors reported no significant difference in the rate of re-intubation between HFNC and NIV.[6] They also noted that fewer subjects in HFNC group required bronchoscopy for secretion management within 48 h after extubation (2 out of 22 vs 9 out of 20, $P = .008$).[6] The evidence to support HFNC in this population based on this study is relatively weak due to the small sample size. Future studies with larger sample sizes are needed to generate more conclusive evidence.

Stable COPD. In 2010, Rea et al[51] compared the use of 12 months of HFNC versus O_2 therapy for 60 subjects with stable COPD or bronchiectasis. Even though the average duration of HFNC was only 1.6 h/d, HFNC was associated with a reduction of COPD exacerbation frequency and days when compared to O_2 therapy (Table 6). Additionally, a cost analysis showed that HFNC was a moderately cost-effective measure for moderate to severe COPD or bronchiectasis.[52] In 2018, Storgaard et al[21] reported that the use of HFNC for 6 h/d for 12 months significantly reduced COPD exacerbations (3.12 vs 4.95/subject annually, $P <$ .001) and improved quality of life. In the 2 short-term cross-over RCTs with 6 weeks of HFNC versus 6 weeks of O_2 therapy or NIV, HFNC was noted to be superior over O_2 therapy in improving CO_2 retention and quality of life,[53] whereas it was noninferior to NIV on improving CO_2 retention.[3]

During Exercise. In 2016, Cirio et al[54] implemented a cross-over RCT to compare HFNC with air-entrainment mask at the same F_{IO_2} for 12 subjects with stable severe COPD during constant loading tests. The authors reported higher oxygen saturations with HFNC at 55–60 L/min than

Table 6. Clinical RCTs Comparing Long-Term Use of HFNC and O_2 Therapy/NIV for Subjects With Stable COPD

Study	Study Type	Subjects, *N*	Indication	Study Duration	Device Use (h/d)	HFNC, L/min	Control	Exacerbation*	Quality of Life	Gas Exchange
Rea et al[51]	RCT	108	COPD ($n = 63$), bronchiectasis	12 mo	1.6	20–25	O_2 therapy	2.97 vs 3.63 ($P = .067$)	NA	NA
Storgaard et al[21]	RCT	138	COPD with chronic hypoxemic respiratory failure	12 mo	6	45–60	O_2 therapy	3.12 vs 4.95 ($P < .001$)	HFNC improved mMRC and SGRQ scores, 6MWT	NA
Nagata et al[53]	Cross-over RCT	29	Stable hypercapnic COPD	12 wk	7.1 ± 1.5, 8.6 ± 2.9	30–40	O_2 therapy	NA	Improved the mean total SGRQ-C score	HFNC improved P_{aCO_2} and pH
Bräunlich et al[3]	Cross-over RCT	94	COPD with stable daytime hypercapnia	12 wk	5.2 ± 3.3 (HFNC), 3.9 ± 2.5 (NIV)	20	NIV	NA	HFNC and NIV both improved SGRQ scores	Both HFNC and NIV decreased P_{CO_2} from baseline; no difference in P_{CO_2} change

* Number of exacerbations per subject per year.
RCT = randomized, controlled trial
HFNC = high-flow nasal cannula
O_2 therapy = conventional oxygen therapy
NIV = noninvasive ventilation
NA = not applicable
mMRC = modified Medical Research Council dyspnea scale
SGRQ = St George Respiratory Questionnaire
6MWT = 6-min walk test

with the air-entrainment mask (95 ± 3% vs 89 ± 3%, respectively, $P < .005$), and endurance time was increased by 41 ± 36% with HFNC.[54] In 2019, Prieur et al[9] published a similar study that enrolled 19 subjects with severe to very severe COPD following exacerbation. The study participants used either HFNC or O_2 therapy during constant work-rate exercises. The authors reported that there were no improvements in endurance time or symptoms, such as dyspnea and leg discomfort, with HFNC utilization.[9] They did note, however, that transcutaneously measured partial pressure of carbon dioxide and heart rate during exercises were lower in the HFNC group than in the group receiving O_2 therapy.[9] The main differences between these 2 studies were the oxygen device in the control group and the S_{pO_2} goal during exercises. In the study by Cirio et al,[54] an air-entrainment mask was utilized with the same F_{IO_2} as HFNC. However, because the S_{pO_2} was lower in the air-entrainment mask group than in the HFNC group at 55–60 L/min during exercise,[54] it suggests that the actual F_{IO_2} was lower due to the air entrainment during exercises due to increased inspiratory flow demand by the subject.[55,56] In contrast, Prieur et al[9] allowed for flow titration when a standard nasal cannula was utilized in the control group, with a titration goal of $S_{pO_2} \geq 90\%$ during exercise.[9] As such, desaturation during exercise might explain the reduced endurance time in the control group in the study by Cirio et al.[54] Interestingly, Prieur et al[9] reported a trend toward lower endurance time in the HFNC group. The authors hypothesized that HFNC therapy at 60 L/min in their study might cause dynamic hyperinflation,[9] which could ultimately limit exercise endurance; this hypothesis still requires more physiological studies to confirm.

Using ROX Index to Predict HFNC Initiation and Separation Success

Little attention was paid to the prediction of the success of HFNC initiation and separation until 2016. Roca et al[57] introduced the concept of using an index that combines oxygenation and breathing frequency to predict HFNC success. They enrolled 157 subjects with severe pneumonia treated with HFNC at 2 centers in the 4-y prospective cohort study.[57] The ratio of S_{pO_2}/F_{IO_2} to breathing frequency, known as the ROX index, was used to predict the need to switch from HFNC to mechanical ventilation. By using the Cox proportional hazards model, Roca et al[57] reported that the cutoff point of the ROX index was 4.88 at 12 h of HFNC. This suggests that a ROX index > 4.88 after being treated with HFNC for 12 h might indicate a higher possibility of HFNC success.[57] After the study was published, the investigators organized a multi-center observational cohort study with a larger sample size to validate their findings.[58] In addition to the consistency of ROX > 4.88 to predict HFNC success, they further explored the cutoff values for ROX to predict HFNC failure after 2, 6, and 12 h of HFNC treatment. They observed that HFNC failure was likely if the ROX index was > 2.85, 3.47, or 3.85 at 2, 6, and 12 h, respectively.[58] Similarly, Zemach et al[59] reported that an increased ROX index was the only independent predictor of HFNC success in their multivariate analysis. This suggests that patients with a low ROX index or with little incremental change of ROX index over time might need earlier and more frequent interventions. Future clinical studies with deliberate treatment algorithms guided by the ROX index are needed. With regard to weaning and liberation from HFNC, Rodriguez et al[60] investigated the ROX index to predict successful separation from HFNC in a retrospective study. They reported that HFNC was successfully removed from 88% (168 out of 190) of subjects in their study at the first attempt, and a $F_{IO_2} \leq 0.4$ and ROX ≥ 9.2 were predictive of HFNC separation success.[60]

An important consideration regarding the ROX index is that it is affected by the HFNC gas flow. When gas flow was increased from 30 to 60 L/min in the study by Mauri et al,[61] 70% of the ROX indexes increased while the remaining subjects had an unchanged or decreased ROX index. Modifications to a typical HFNC setup may also affect oxygenation. Duprez et al[62] reported that placing a double-trunk mask over the HFNC nasal prongs in an attempt to reduce room air entrainment can improve oxygenation. In 15 different subjects with acute refractory hypoxemia, with flows set at 51 ± 6 L/min, P_{aO_2} improved from 68 ± 14 mm Hg to 85 ± 22 mm Hg ($P < .001$) after adding the double-trunk mask.[62] These findings might indicate the need to modify the ROX index by gas flow or modifications to a typical setup.

Other Uses of HFNC: Trans-Nasal Aerosol Pulmonary Delivery

Removing HFNC to deliver traditional aerosol therapy reduces the benefits of HFNC. Placing a face mask with nebulizer over the HFNC may result in the substantial reduction of the intended inhaled dose.[63] As such, placing a nebulizer in-line with HFNC has become a delivery route of interest.[64,65] Concerns have been raised about the inhaled dose via the trans-nasal aerosol delivery method. Two recently published cross-over RCTs reported that albuterol delivery at regular flow settings (30–35 L/min) for subjects with stable COPD and asthma could generate similar bronchodilation responses as a jet nebulizer with a mouthpiece/mask.[19,20] Li et al[66] further explored the dose-response relationship among 42 subjects with stable COPD and asthma. In their study, the investigators reported that 1.5 mg albuterol delivered via HFNC at 15–20 L/min elicited similar bronchodilation effects as 400

μg albuterol via pressurized metered-dose inhaler and spacer.[66]

For patients who need to inhale aerosolized medication continuously for long periods of time (ie, > 2 h), such as inhaled albuterol for those with severe asthma[67] or inhaled epoprostenol for patients with pulmonary hypertension,[68,69,70] traditional aerosol delivery such as jet nebulizer via mask/mouthpiece is challenging. Continuous transnasal aerosol delivery via HFNC offers a feasible solution to reduce the inconvenience and discomfort associated with traditional aerosol delivery setups. Two retrospective studies reported improvement in oxygenation when inhaled epoprostenol was delivered via HFNC.[68,69] Titrating flow to be lower than subject inspiratory flow was found to generate more evident responses of inhaled epoprostenol than using constant flow.[70] However, the evidence to support the use of continuous aerosol delivery via HFNC is still weak due to the retrospective nature and small sample size of these studies. Also, the overall safety of delivering pulmonary vasodilators via the nasal route warrants more investigation.

Summary

There have been many advances in the utilization of HFNC therapy for adult patients in the past 2 years. Results from high-quality RCTs support the use of HFNC therapy for patients with acute hypoxemic respiratory failure and patients with planned extubation compared to O_2 therapy. HFNC is also favorable for long-term use for patients with hypercapnic COPD. Evidence also supports the use of HFNC during endoscopy and for preoxygenation before intubation. However, cost-effectiveness still needs to be considered in both of these applications. There is also some emerging evidence that supports the combined use of NIV and HFNC to facilitate weaning patients at high risk for extubation failure. The ROX index may be a useful tool to predict the successful initiation or separation of HFNC, but further studies are needed. Evidence for the use of HFNC for postsurgical patients and for patients with severe COPD during exercise remains controversial and also warrant more studies. There are currently no guidelines regarding the use of HFNC for various disease states, but, due to the widespread use, there is an apparent need.

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