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Review

Physiological effects and clinical evidence of high-flow nasal cannula during acute exacerbation in COPD patients: A narrative review

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide. During severe exacerbations, COPD patients may develop acute respiratory failure (ARF), often necessitating hospital admission due to impaired gas exchange. In COPD patients, the diaphragm is subjected to an increased workload resulting from airflow limitations and geometric changes in the thorax due to pulmonary hyperinflation. Noninvasive ventilation (NIV) plays a crucial role in managing type II ARF by improving alveolar ventilation, reducing the work of breathing, minimizing the need for endotracheal intubation (ETI), and decreasing both hospital stays and mortality rates. Studies have shown that approximately 64% of patients with acute exacerbation of COPD (AECOPD) may fail NIV, primarily due to worsening respiratory function, interface intolerance, cardiovascular instability, or neurological deterioration. For patients intolerant to NIV, a trial with a high-flow nasal cannula (HFNC) is recommended. Recently, HFNC has gained popularity as a novel respiratory support system and is increasingly used in routine clinical practice for AECOPD patients. It delivers warmed, humidified, and oxygen-enriched air through a nasal cannula at flow rates of up to 60 L/min. This narrative review aims to describe the physiological effects of HFNC in the COPD population and provide an updated overview of HFNC's role in AECOPD patients requiring hospitalization.

Introduction

Chronic obstructive pulmonary disease (COPD) is among the leading causes of death worldwide.[1] Characterized by expiratory airflow limitation, COPD leads to symptoms of dyspnea, cough, and sputum production. Patients with worsening symptoms may experience exacerbations, often triggered by an upper respiratory tract infection.[2] In cases of severe exacerbation, COPD patients may develop acute respiratory failure (ARF), requiring hospital admission due to impaired gas exchange,[3] which may present as hypoxemia, hypercapnia, or a mixed disorder.

In cases of exclusive hypoxemia, standard oxygen therapy (such as a low-flow nasal cannula, venturi mask, or reservoir mask) may suffice. However, in 20% of patients, respiratory acidosis and carbon dioxide (CO_2) retention may occur due to increased work of breathing (WOB).[4] In COPD patients, the diaphragm must work against a heightened load caused by airflow limitation and thoracic geometric changes from pulmonary hyperinflation.[5]

Noninvasive ventilation (NIV) plays an essential role in managing type II ARF, as it improves alveolar ventilation, reduces WOB, decreases the need for endotracheal intubation (ETI), and lowers both hospital stays and mortality rates.[6]

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Recently, guidelines from the European Respiratory Society (ERS) and American Thoracic Society (ATS) have recommended NIV for stable hypercapnic chronic COPD patients, aiming to reduce or normalize carbon dioxide arterial pressure ($PaCO_2$).[7,8] Hypercapnic respiratory failure is a known indicator of increased mortality risk.[9,10] Although NIV generally has a high success rate in these patients,[11] it is not always effective. In addition to exacerbation severity, NIV intolerance is a major contributor to NIV failure.[12]

In cases of NIV intolerance, a trial with a high-flow nasal cannula (HFNC) may be considered.[13,14] HFNC has recently gained attention as a novel form of noninvasive respiratory support and is increasingly used in routine clinical practice.[15] HFNC delivers warmed, humidified, and oxygen-enriched air through a nasal cannula at flow rates of up to 60 L/min.[16] In addition, HFNC can be combined with vibrating mesh nebulizers to deliver aerosol therapy without impairing respiratory support performance.[17]

This narrative review aims to describe the physiological effects of HFNC in the COPD population and provide an update on the role of HFNC in acute exacerbation of COPD (AECOPD) patients requiring hospitalization.

Methods

We searched bibliographic databases including Institute for Scientific Information Web of Science, Medline via PubMed, Science Direct, Scopus, Wiley Online Library, Google Scholar, and other international databases and websites for published articles with abstracts. The keywords used in the search were “High-Flow Nasal Cannula,” “High-Flow Nasal Oxygen Therapy,” “COPD,” and “AECOPD.” The search was limited to journal articles written in English and published between 2010 and 2024.

Inclusion Criteria: Initial selection was based on the titles and abstracts of the articles. Relevance was further assessed by reviewing the full-text versions. Case reports and abstracts were excluded. Articles included had to meet at least one of the following criteria: (1) HFNC use during AECOPD, (2) HFNC use in COPD patients with ARF, or (3) HFNC use during COPD hospitalization.

Physiological Effects of HFNC on COPD and AECOPD Patients

A unique feature of HFNC is its ability to deliver high flows of heated, humidified gas (20–60 L/min) with an inspired fraction of oxygen (FiO_2) range of 0.21–1.0.[18] The physiological responses to HFNC include increases in mean airway pressure, end-expiratory lung volume (EELV), and oxygenation, with optimal effects generally achieved at higher flows (40–60 L/min).[19] Effects on dead space washout, WOB, and respiratory rate (RR) may occur at lower flows (20–45 L/min).[20] Here, we describe the physiological effects in COPD patients based on their respiratory pathophysiology (Figure 1).

Mucociliary clearance

Cold, dry gas can negatively affect ARF patients. Conventional oxygen therapy (COT) devices are associated with discomfort, such as mask-related irritation, nasal and oral dryness, eye irritation, and, in some cases, gastric distension.[21] Additionally, airway resistance increases to protect the lungs from cold, dry air, thus reducing airflow in the upper airways and trachea.[22,23]

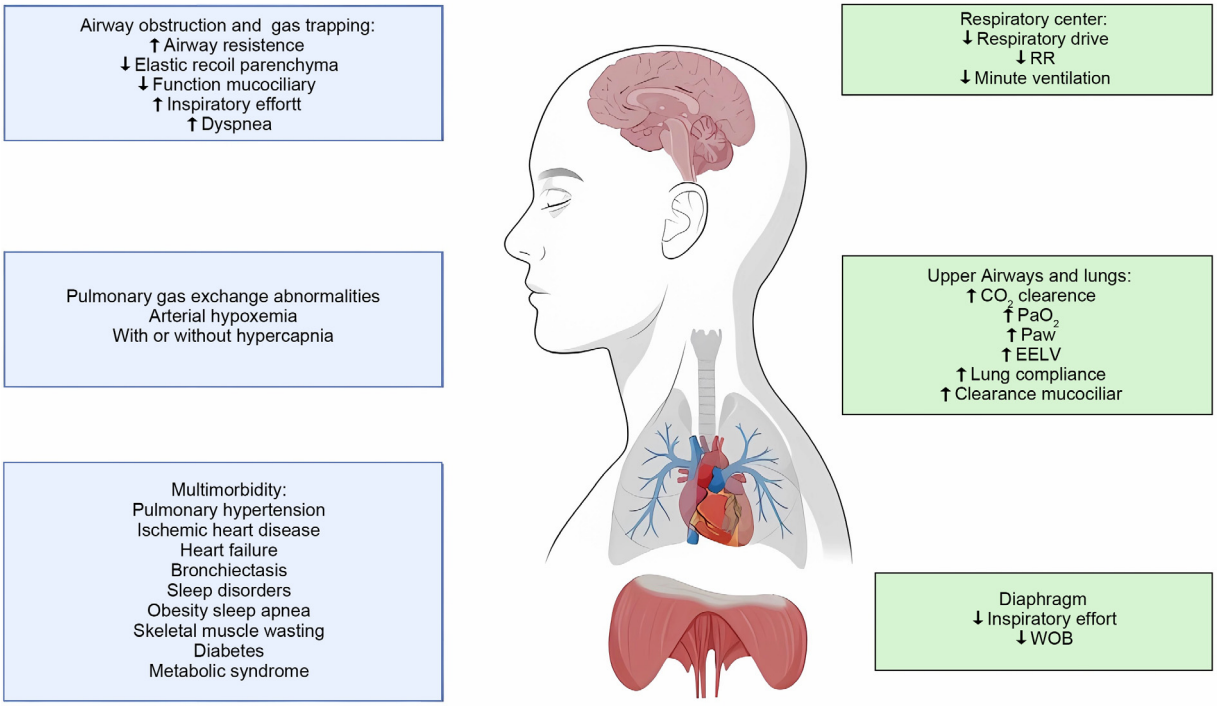

Figure 1. Physiological effects of high flow nasal cannula in COPD subjects based on their respiratory pathophysiology. CO_2: Carbon dioxide; EELV: End-expiratory lung volume; COPD: Chronic obstructive pulmonary disease; RR: Respiratory rate; PaO_2: Carbon dioxide arterial pressure; WOB: Work of breathing

A study by Rea et al.[24] investigated whether long-term HFNC (20–25 L/min at 37 °C) could improve clinical outcomes over standard care in COPD or bronchiectasis patients. This single-center, prospective study of 108 patients demonstrated that patients receiving HFNC for 12 months experienced a significantly longer time to exacerbation (18.2 days *vs.* 33.5 days, *P*=0.045), a longer duration until the first exacerbation (median 52 days *vs.* 27 days, *P*=0.0495), and a reduced exacerbation rate (2.97/patient/year *vs.* 3.63/patient/year, *P*=0.067) compared with the standard care group, despite a relatively low average daily HFNC use (1.6 h/day).

Dead space washout

Approximately one-third of tidal volume is rebreathed from anatomical dead space. At the end of expiration, dead space is filled with oxygen-depleted (15%–16%) and CO_2-rich (5%–6%) gas.[25]

HFNC reduces the rebreathed CO_2 volume, potentially allowing either a reduction in tidal volume or RR to maintain alveolar ventilation, thus reducing WOB.[25]

Hypercapnia susceptibility is further influenced by increased dead space, leading to relative alveolar hypoventilation despite an increased respiratory drive.[4] In advanced COPD, physiological dead space (wasted ventilation) is heightened due to underlying ventilation-perfusion ratio mismatch.[26]

In a randomized crossover study, Fraser et al.[27] compared short-term physiological responses between HFNC (30 L/min) and standard oxygen therapy (2–4 L/min) in 30 patients on long-term oxygen therapy (LTOT) (>15 h/day). HFNC reduced transcutaneous carbon dioxide ($TcCO_2$) levels compared with standard oxygen therapy (43.3 mmHg *vs.* 46.7 mmHg, *P* <0.001).

Bräunlich et al.[28] reported that HFNC effectively lowered $PaCO_2$ in stable hypercapnic COPD patients under different experimental conditions (*A*=20 L/min, low leakage, two prongs, both inside; *B* =40 L/min, low leakage, two prongs, both inside; *C*=40 L/min, high leakage, two prongs, one outside and open; *D*=40 L/min; high leakage, two prongs, one outside and closed). These data support the hypothesis that CO_2 elimination during HFNC is more dependent on leakage and airflow than on mean airway pressure. These results align with findings by McKinstry et al.[29] who showed flow-dependent reductions in $TcCO_2$ in stable COPD patients receiving HFNC at varying flow rates (15–45 L/min). Pilcher et al.[30] further demonstrated that short-term HFNC at 35 L/min reduced $TcCO_2$ in AECOPD patients compared with standard oxygen therapy (−1.4 mmHg, 95% confidence interval [CI]: −2.2 to −0.6, *P*=0.001).

Decreased WOB

COPD patients with increased dead space require higher minute ventilation to maintain alveolar ventilation and stable $PaCO_2$. While these compensatory mechanisms may suffice when the disease is stable, they may become inadequate during exacerbation or physical exertion.

Pisani et al.[31] studied HFNC and NIV's effects on inspiratory effort in stable hypercapnic COPD patients, measuring transdiaphragmatic pressure, respiratory pattern, and gas exchange. Fourteen patients with stable COPD and hypercapnia underwent five trials lasting 30 min each: HFNC at two flow rates (20 L/min and 30 L/min), both with the mouth open and closed, and NIV, applied in a random order. After each trial, standard oxygen therapy was reinstated for 10 min. Compared with baseline, HFNC and NIV significantly improved the breathing pattern and reduced inspiratory effort, as indicated by a decrease in RR and reduction in Pdi swing (transdiaphragmatic pressure). These findings on inspiratory effort are in line with the results of Longhini et al.[32] who performed a physiological crossover trial in 30 AECOPD patients who received NIV for more than 24 h. All patients underwent five 30-min trials; the first, third, and fifth with NIV, and the second and fourth randomized to standard oxygen therapy and HFNC. Diaphragm displacement (DD) and thickening fraction (TF) were determined by sonographic evaluation at the end of each trial. DD was no different among the trials, whereas TF and RR were higher with standard oxygen therapy. In a preliminary study, Rittayamai et al.[33] evaluated HFNC in 12 hypercapnic COPD patients initially on NIV. Patients underwent HFNC at flow rates from 10 L/min to 50 L/min in 15-min intervals. HFNC at 30 L/min reduced inspiratory effort, assessed by simplified esophageal pressure-time product (sPTPes), comparable with NIV and with greater reduction than at 10 L/min and 20 L/min (*P* <0.001). Respiratory rate (RR) was lower (*P*=0.003), and peripheral oxygen saturation (SpO_2) was higher (*P*=0.028) at 30–50 L/min than at 10 L/min. Application of HFNC at 30 L/min for a short period of time reduced inspiratory effort compared with that at 10 L/min and 20 L/min and produced a similar effect to NIV in hypercapnic COPD with mild-to-moderate exacerbation. Higher flow rates reduce RR but sometimes increase inspiratory effort. In line with these findings, Colaianni-Alfonso observed that HFNC flows above 40 L/min, provided no additional benefit in comfort or respiratory effort reduction in AECOPD patients, as higher flows increased TF and caused discomfort during exhalation.[34]

Clinical Application of HFNC in AECOPD Patients

AECOPD is a recognized risk factor for disease progression, and frequent exacerbations are associated with increased mortality rates.[9] Standard oxygen therapy and NIV are important treatment strategies for select AECOPD patients.[35] NIV is the first-line treatment for AECOPD patients with respiratory acidosis, as it reduces the need for ETI and decreases in-hospital mortality rates.[8] However, whether HFNC can effectively reduce the risks of intubation and mortality, and improve arterial blood gas (ABG) levels in AECOPD patients, remains unclear. Table 1 summarizes the most relevant studies in the clinical setting and their significant findings.

HFNC vs. standard oxygen therapy in AECOPD

While HFNC's superiority over standard oxygen therapy in terms of physiological effects has been demonstrated,[19] clinical evidence remains inconsistent for AECOPD patients.

Li et al.[36] conducted a prospective, randomized controlled trial (RCT) on AECOPD patients with baseline ABG pH ≥7.35, PaO_2 <60 mmHg, and $PaCO_2$ >45 mmHg. The primary endpoint was treatment failure (requirement for NIV or invasive mechanical ventilation [IMV]). In total, 320 patients were randomly assigned to the HFNC group (*n*=160) or the standard oxygen therapy group (*n*=160). During hospitalization, 16 (10.0%) pa-

Table 1
Studies comparing the effectiveness of HFNC *vs.* standard oxygen therapy and NIV in different clinical settings.

Author (year)	Study design	Patients (*n*)	ABGs at admission	HFNC settings	Comparative	Main results
Li et al. (2020)[36]	RCT	320	pH: 7.38 ± 0.03, $PaCO_2$: (54.9 ± 7.1) mmHg	Flow: (33.4 ± 5.6) L/min, FiO_2: 0.28 ± 0.01	Standard oxygen therapy (2–4 L/min)	HFNC group exhibited a lower failure rate; significant reduction in $PaCO_2$ at 24 h.
Xia et al. (2022)[37]	RCT	330	pH ≥7.35, $PaCO_2$ >45 mmHg	Flow: 30 (IQR: 25–40) L/min, FiO_2: 0.32 (IQR: 0.3–0.4)	Standard oxygen therapy (1–5 L/min)	No significant difference in intubation or escalation to NIV between groups.
Lee et al. (2018)[38]	Prospective	88	pH: 7.32 ± 0.03, $PaCO_2$: 54.5 ± 9.6 mmHg	Flow: 35 L/min (up to 45–60 L/min), FiO_2: SpO_2 target (88%–92%)	NIV: IPAP: 10 cmH_2O, EPAP: 5 cmH_2O	No significant differences in 30-day mortality or intubation rates between groups.
Sun et al. (2019)[39]	Retrospective	82	pH: 7.31 (7.29–7.33), $PaCO_2$: 58 (54–62) mmHg	Flow: 50 L/min, FiO_2: SpO_2 target (88%–92%)	NIV: IPAP: 10 cmH_2O, EPAP: 4 cmH_2O	HFNC did not increase treatment failure rates; fewer nursing interventions and skin breakdown in the HFNC group.
Cong et al. (2019)[40]	RCT	168	pH: 7.25 ± 0.08, $PaCO_2$: (72.11 ± 16.31) mmHg	Flow: 30–35 L/min, FiO_2: SpO_2 target (88%–92%)	NIV: IPAP: 10 cmH_2O, EPAP: 5 cmH_2O	No significant differences in ABGs; lower complications and increased comfort and nursing satisfaction with HFNC.
Cortegiani et al. (2020)[41]	RCT	79	pH: 7.30 ± 0.03, $PaCO_2$: (73.7 ± 12.8) mmHg	Flow: 60 L/min, FiO_2: SpO_2 target (88%–92%)	NIV: PSV: Adjust 6–8 mL/kg of IBW, PEEP: 5 cmH_2O	HFNC was statistically non-inferior to NIV in reducing $PaCO_2$ after 2 h; 32% of HFNC patients required an NIV switch.
Wang et al. (2023)[42]	Retrospective: Propensity Score-Matched	88	pH: 7.34 ± 0.08, $PaCO_2$: (69.6 ± 20.7) mmHg	Flow: (48.3 ± 8.6) L/min, FiO_2: 39.9 ± 0.2	NIV: IPAP: (19 ± 3.2) cmH_2O, EPAP: (6.3 ± 1.8) cmH_2O	No differences in 30-day and 90-day mortality; shorter ICU stay and LOS in HFNC group; NT-proBNP was a factor for HFNC failure.
Jing et al. (2019)[43]	RCT (Post-extubation patients)	42	pH: 7.46 ± 0.04, $PaCO_2$: (53.2 ± 6.7)mmHg	Flow: (52.4 ± 6.3) L/min, FiO_2: 0.4 ± 0.1	NIV: IPAP: (11.4 ± 2.0) cmH_2O, EPAP: (4.6 ± 0.5) cmH_2O	HFNC improved secretion clearance and patient comfort.
Tan et al. (2020)[44]	RCT (Post-extubation patients)	86	pH: 7.48 (IQR: 7.42–7.51), $PaCO_2$: 50.5 (IQR: 48–57.8) mmHg	Flow: 50 L/min, FiO_2: SpO_2 target (88%–92%)	NIV: IPAP: 8 cmH_2O, EPAP: 4 cmH_2O	No significant difference in reintubation rates; better tolerance and comfort with HFNC.
Thille et al. (2021)[45]	RCT (Post-extubation patients)	150	pH: 7.45 ± 0.05, $PaCO_2$: (44 ± 9) mmHg	Flow: (50 ± 3) L/min, FiO_2: 0.42 ± 0.13	NIV: PSV: (7.9 ± 2.4) cmH_2O, PEEP: (5.2 ± 1.3) cmH_2O	NIV combined with HFNC during breaks decreased reintubation compared to HFNC alone

ABGs: Arterial blood gases; EPAP: Expiratory positive airway pressure; FiO_2: Inspired fraction of oxygen; HFNC: High-flow nasal cannula; IBW: Ideal body weight; ICU: Intensive care unit; IPAP: Inspiratory positive airway pressure; LOS: Length of stay; NIV: Non-invasive ventilation; NT-proBNP: N-terminal pro-B-type Natriuretic Peptide; $PaCO_2$:Carbon dioxide arterial pressure; PEEP: Positive end-expiratory pressure; PSV: Pressure support ventilation; RCT: Randomized controlled trial; SpO_2: Peripheral saturation of oxygen.

tients in the HFNC group experienced treatment failure, which was significantly lower than the 31 (19.4%) patients in the standard oxygen therapy group (P = 0.026). After 24 h, $PaCO_2$ in the HFNC group was lower than in the standard oxygen therapy group ([54.1±9.79] mmHg *vs.* [56.9±10.1] mmHg, P=0.030). $PaCO_2$ > 59 mmHg after 24 h of HFNC was identified as an independent risk factor for treatment failure (odds ratios [OR]=1.078, 95% CI: 1.006–1.154, P=0.032).

Conversely, Xia et al.[37] conducted an RCT in 16 tertiary hospitals in China, randomly assigning AECOPD patients with baseline pH ≥ 7.35 and $PaCO_2$ > 45 mmHg to either HFNC or standard oxygen therapy, with the primary endpoint being treatment failure requiring IMV. In total, 330 patients completed the trial. In the HFNC group, 4 of 158 patients met the criteria for intubation, compared with 1 of 172 in the standard oxygen therapy group (P = 0.198). The number of patients who escalated to NIV was comparable in both groups (HFNC: 15 [9.5%] *vs.* standard oxygen therapy: 22 [12.8%], P=0.343). This multicenter RCT concluded that HFNC did not reduce the need for intubation in AECOPD patients with mild hypercapnia.

Another frequent clinical setting is the process of extubation in patients who received IMV from AECOPD. Di Mussi et al.[46] randomized 14 COPD patients recovering from an exacerbation episode to receive HFNC or standard oxygen therapy after extubation.HFNC significantly reduced the WOB and respiratory drive, demonstrating superiority over standard oxygen therapy in the post-extubation setting.

A recent meta-analysis showed that compared with standard oxygen therapy, short-term HFNC reduced $PaCO_2$ and the need for increased ventilatory support in acute hypercapnic COPD, while long-term HFNC reduced COPD exacerbation rates in chronic hypercapnia. HFNC thus holds the potential for treating hypercapnic COPD.[47]

HFNC vs. NIV in AECOPD

To date, NIV is the cornerstone treatment for managing AECOPD patients (pH <7.35 and $PaCO_2$ > 45 mmHg). However, several factors may contribute to NIV failure, including discomfort related to the interface, patient–ventilator interaction, airway secretions, disease severity, and caregiver expertise. Recent data indicate that HFNC may also play a role in managing AECOPD patients.[48] In a prospective observational study by Lee et al.[38] researchers evaluated the effectiveness of HFNC *vs.* NIV in AECOPD patients (pH 7.25–7.35 mmHg and $PaCO_2$ >45 mmHg). This study enrolled 88 patients, with the primary endpoint being to assess the rate of ETI and 30-day mortality between the HFNC group (n=44) and the NIV group (n=44),

although the criteria for group assignment were unclear. No significant differences were found in ETI requirements (HFNC 25.0% *vs.* NIV 27.3%, *P*=0.857) or 30-day mortality (HFNC 15.9% *vs.* NIV 18.2%, *P*=0.845). Similarly, ABG measurements showed no differences between groups at 6 h and 24 h of treatment. These findings align with those of Sun et al.[39] who conducted a retrospective observational study comparing HFNC and NIV effectiveness in AECOPD patients (pH ≤ 7.35 and $PaCO_2$ ≥ 50 mmHg). In this study, which included 82 patients, the primary endpoint was ETI rate between the two groups (HFNC, *n*=39 *vs.* NIV, *n*=43). No statistically significant differences were noted in the ETI rates (HFNC 28% *vs.* NIV 39.5%; *P* = 0.268), or in the need for switching between interventions (HFNC to NIV or vice versa). Additionally, 28-day mortality did not differ significantly between groups (HFNC 15.4% *vs.* NIV 14%; *P*=0.824). During the first 24 h, patients in the HFNC group required significantly fewer nursing airway interventions, experienced better tolerance, and had fewer facial injuries than those in the NIV group.

However, NIV intolerance frequently occurs, increasing NIV failure rates, intubation rates, and overall mortality. In a research letter, Bräunlich and Wirtz[49] reported on 38 AECOPD patients (pH <7.38, $PaCO_2$: 67.6 mmHg) who were unable to tolerate NIV. They observed a significant reduction in $PaCO_2$ (*P*=0.001) and a significant correction of pH (*P* <0.0001) after a mean HFNC application time of 195 min. Despite its retrospective nature and lack of a control group, this investigation, though limited in patient numbers, provides initial support for HFNC's potential usefulness in managing hypercapnic AECOPD.

Cong et al.[40] conducted a single-blinded RCT to compare the efficacy of HFNC and NIV in hospitalized AECOPD patients, focusing on comfort and satisfaction outcomes. A total of 168 patients were randomized equally to receive either HFNC or NIV. Key exclusion criteria included pneumonia, acute heart failure, and particularly, acute respiratory acidosis requiring NIV. The study's primary aim was to evaluate changes in ABGs at 12 h and 5 days post-treatment. No significant differences in ABG were observed between groups; however, the HFNC group experienced fewer complications and reported higher comfort and satisfaction scores. Limitations included unclear inclusion criteria related to blood gas parameters, COPD severity, and degree of respiratory acidosis, making it challenging to characterize the study population.

In a notable retrospective study, Wang et al.[42] conducted a propensity score-matched analysis in 88 AECOPD patients, reporting a 38.6% failure rate in those receiving HFNC as a first-line treatment, who subsequently required rescue NIV. The findings showed no differences in mortality or need for IMV between patients receiving rescue NIV and those who received NIV as the initial treatment. Additionally, the HFNC group had fewer intensive care unit (ICU) and hospital days and incurred lower overall costs. Elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were identified as a significant predictor of HFNC treatment failure.

In a more recent study, Veenstra et al.[50] identified a significant association between cardiac (myocardial infarction, heart failure, or arrhythmia) (OR=0.435, *P*=0.013) and vascular (hypertension and peripheral arterial disease) comorbidities (OR=0.493, *P*=0.035) and a lower likelihood of HFNC success in AECOPD patients. The study aimed to investigate the reasons for initiating HFNC in COPD patients experiencing exacerbations, with sputum stasis being the most frequently reported indication for HFNC initiation.

In the era of RCTs, a study by Cortegiani et al.[41] was published in 2019 to assess the non-inferiority of HFNC compared with NIV in measuring $PaCO_2$ reduction in AECOPD and mild-to-moderate respiratory acidosis patients (pH 7.25–7.35 mmHg and $PaCO_2$ ≥55 mmHg). The trial randomized 80 patients, finding that HFNC was non-inferior to NIV regarding $PaCO_2$ reduction. However, one-third of the patients in the HFNC group switched to NIV within 6 h of randomization, primarily due to a lack of improvement in gas exchange. The HFNC group included participants with a body mass index (BMI) greater than 30 kg/m^2, which is noteworthy as some patients may present with obesity hypoventilation syndrome (OHS) or obstructive sleep apnea (OSA). This clinical situation may indicate overlapping syndromes (OSA or OHS plus COPD). Pisani et al.[51] evaluated the acceptability of HFNC and its efficacy in reducing $PaCO_2$ levels in patients recovering from an episode of AECOPD with continuing hypercapnia but without acidosis (pH >7.35 mmHg and $PaCO_2$ >45 mmHg). These subjects received HFNC treatment for 8 h/day and overnight. Patients were categorized into "pure" COPD *vs.* COPD/OSA, and a significant reduction in $PaCO_2$ was observed (*P* = 0.044). Furthermore, the subset of patients with lower pH at enrollment showed the best response in terms of CO_2 elimination. HFNC significantly decreased $PaCO_2$ levels after 72 h only in "pure" COPD patients.

In a recent RCT, Tan et al.[52] studied 225 patients with acute moderate hypercapnic respiratory failure (pH 7.25–7.35 mmHg and $PaCO_2$ ≥ 50 mmHg) admitted to the ICU. They reported a treatment failure rate of 25.7% in the HFNC group compared with 14.3% in the NIV group, concluding that HFNC was not shown to be non-inferior to NIV and resulted in a higher incidence of failure when used as the initial respiratory support. The most common reason for treatment failure in the HFNC group was the aggravation of carbon dioxide retention. The study did not report BMI or comorbidities such as OSA or OHS, which could contribute to hypoventilation.

The weaning process in AECOPD patients presents a significant clinical challenge. Compared with IMV, treatment with NIV in AECOPD patients is associated with lower in-hospital mortality, reduced length of hospital stays, and lower healthcare costs.[11] Jing et al.[43] conducted a single-center RCT involving COPD patients who were intubated for acute exacerbation and hypercapnia ($PaCO_2$ >45 mmHg) at extubation. They enrolled 42 patients to compare the effectiveness of HFNC (*n*=22) and NIV (*n*=20). The primary aim was to measure ABGs and vital signs at 3, 24, and 48 h after extubation. At 3 h post-extubation, the pH in the NIV group was lower than that in the HFNC group (7.42±0.06 *vs.* 7.45±0.05, *P*=0.010). At 24 h post-extubation, the mean arterial pressure ([82.97±9.04] *vs.* [92.06±11.11] mmHg, *P*=0.050) and pH (7.42±0.05 *vs.* 7.46±0.03, *P*=0.050) in the NIV group were also lower than those in the HFNC group. No significant differences were found at 48 h post-extubation. The HFNC group reported better comfort scores (3.55±2.01 *vs.* 5.15±2.28, *P*=0.020), and fewer patients required bronchoscopy for secretion management within 48 h post-extubation (2/22 *vs.* 9/20, *P*=0.030). HFNC presents a potential alternative to NIV for weaning hypercap-

nic COPD patients, as it enhances vital signs and ABGs while improving patient comfort and facilitating secretion clearance.

In light of the increasing use of HFNC during extubation and consistent with previous reports, Tan et al.[44] conducted a multicenter RCT aimed at proving the non-inferiority of HFNC in preventing post-extubation failure in COPD patients intubated for type II ARF. Forty-four patients were randomly assigned to the HFNC group and 42 to the NIV group. The treatment failure rate in the HFNC group was 22.7%, compared with 28.6% in the NIV group (P=0.535). Analysis of treatment failure causes indicated that treatment intolerance in the HFNC group was significantly lower than that in the NIV group (P=0.015). Twenty-four hours after extubation, the RR in the HFNC group had returned to baseline, while the NIV group remained elevated. The comfort score and incidence of nasal and facial skin breakdown were significantly better in the HFNC group than in the NIV group (median=7, [interquartile range: 6–8] *vs.* median=5, [interquartile range: 4–7], $P < 0.001$, and 0% *vs.* 9.6%, $P = 0.027$, respectively). The use of HFNC after extubation did not result in increased rates of treatment failure compared with NIV, and HFNC also demonstrated better tolerance and comfort than NIV.

A recent systematic review and meta-analysis confirm these findings, concluding that HFNC can serve as an alternative treatment to NIV after extubation in AECOPD and hypercapnia patients. However, in patients without hypercapnia, HFNC is less effective than NIV.[53] Another attractive concept is the use of combined therapy, specifically using HFNC during NIV breaks. Thille et al.[45] conducted a post-hoc analysis of a multicenter RCT that compared NIV plus HFNC (NIV+HFNC) *vs.* HFNC alone immediately after extubation. A total of 150 subjects with COPD were recruited, with 86 patients treated with NIV alternating with HFNC and 64 patients receiving HFNC alone included in the analysis. The reintubation rate was 13% (11 of 86 patients) in the NIV+HFNC group and 27% (17 of 64 patients) in the HFNC alone group (P=0.03). This demonstrates a significantly lower reintubation rate with NIV+HFNC than with HFNC alone at 72 h. ICU mortality did not differ between groups, with rates of 6% (5/86) for NIV+HFNC *vs.* 9% (6/64) for HFNC alone (P=0.40). Another recent retrospective study produced similar results, concluding that there was no significant difference between subjects receiving NIV combined with HFNC and those receiving NIV with standard oxygen therapy. According to Schroeder et al.[54] the combination of NIV and HFNC does not appear to provide any additional benefits over NIV combined with standard oxygen therapy concerning 30-day mortality and the need for intubation. There are still questions to be addressed regarding the use of HFNC in subjects with AECOPD; however, its physiological and clinical benefits do not appear to negatively impact these patients.[55]

Conclusions

The recommendation for NIV as the first-line treatment in subjects with AECOPD remains clear. Nevertheless, physiological studies regarding the use of HFNC in AECOPD patients have demonstrated positive outcomes that translate into clinical practice. HFNC may serve as a viable alternative for patients intolerant to NIV, during NIV breaks, and in the post-extubation period for COPD patients with hypercapnia. However, further research is essential to tailor this treatment approach and identify which patients are most likely to benefit from HFNC therapy.

CRediT Authorship Contribution Statement

Nicolás Colaianni-Alfonso: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Data curation, Conceptualization. **Federico Herrera:** Writing – review & editing, Writing – original draft, Validation, Formal analysis. **Diego Flores:** Writing – review & editing, Writing – original draft, Data curation. **Cristian Deana:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Mina Vapireva:** Writing – review & editing, Writing – original draft, Data curation. **Daniele Guerino Biasucci:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Salvatore Maurizio Maggiore:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Luigi Vetrugno:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

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Ethics Statement

Not applicable.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper interest.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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