Journal of Clinical and Nursing Research, 2025, Volume 9, Issue 11
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Analysis of the Efficacy of High-Flow Nasal Cannula Oxygen Therapy and Non-Invasive Ventilation in COPD Patients

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Abstract: Patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) often suffer from respiratory failure and require respiratory support therapy. High-flow nasal cannula oxygen therapy (HFNC) and non-invasive positive pressure ventilation (NIPPV) are commonly used non-invasive respiratory support methods. HFNC can provide precisely heated and humidified high-flow oxygen, reducing dead space and increasing alveolar ventilation. NIPPV can supply stable high-concentration oxygen and improve gas exchange. This article reviews the application of HFNC and NIPPV in the acute exacerbation stage of COPD, aiming to provide references for reasonable clinical selection.

Keywords: Chronic obstructive pulmonary disease; High-flow nasal cannula oxygen therapy; Non-invasive ventilation; Acute exacerbation stage

Online publication: Dec 10, 2025

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation, usually caused by airway and/or alveolar abnormalities resulting from exposure to toxic particles or gases [1]. The acute exacerbation stage of COPD refers to a sustained deterioration in the patient's condition beyond their daily state, necessitating a change in the routine medication for underlying COPD. The condition often progresses rapidly and can be complicated by respiratory failure, posing a serious threat to the patient's life and health [2]. Timely and effective respiratory support therapy is crucial for improving the prognosis of patients with acute exacerbation of COPD. High-flow nasal cannula oxygen therapy (HFNC) and non-invasive positive pressure ventilation (NIPPV) are two important non-invasive respiratory support modalities that play a pivotal role in the treatment of acute exacerbations of chronic obstructive pulmonary disease (COPD). However, there are certain differences between the two in terms of efficacy, applicable

populations, and other aspects. A thorough understanding of the application of HFNC and NIPPV during acute exacerbations of COPD can assist clinicians in formulating more precise and effective treatment plans for patients.

2. Pathophysiological changes during acute exacerbations of COPD

During acute exacerbations of COPD, multiple factors lead to a significant increase in airway inflammatory responses in patients. Viral or bacterial infections are common triggers, which can promote the aggregation of inflammatory cells such as neutrophils and macrophages in the airways, releasing a large number of inflammatory mediators, such as tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) [3]. These inflammatory mediators cause congestion and edema of the airway mucosa, as well as hypersecretion of mucus, leading to airway narrowing and further exacerbation of airflow limitation [4]. Simultaneously, inflammation damages the normal function of airway cilia, obstructing the expulsion of sputum and exacerbating ventilation disorders.

COPD patients inherently experience a decrease in lung elastic recoil and premature closure of small airways, resulting in gas retention during exhalation and pulmonary hyperinflation. During acute exacerbations, the aforementioned pathological changes intensify, leading to a further increase in residual volume and more pronounced dynamic pulmonary hyperinflation [5]. This not only increases the work of the respiratory muscles, leading to respiratory muscle fatigue, but also elevates intrathoracic pressure, affecting cardiac diastolic function and further exacerbating the respiratory and circulatory burden. Due to airway obstruction and mismatched ventilation/perfusion ratios in the lungs, patients experience ventilation dysfunction, with impaired carbon dioxide excretion and insufficient oxygen intake, resulting in hypoxemia with or without hypercapnia, namely respiratory failure. Severe respiratory failure can trigger a series of complications, such as pulmonary encephalopathy and arrhythmias, endangering the patient's life.

3. HFNC

3.1. Working principle of HFNC

HFNC precisely adjusts the inhaled oxygen concentration through an air-oxygen blender. Its high-flow gas delivery device can provide a gas flow rate of up to 80 L/min, which far exceeds the peak inspiratory flow rate of patients' spontaneous breathing. This ensures that patients receive a stable, high-flow gas supply throughout the inspiratory process, maintaining a constant inhaled oxygen concentration [6]. Before delivery, the gas passes through a warming and humidifying device, where it is heated to 31–37°C and humidified to a level of 33–44 mg/L, closely approximating the temperature and humidity of the gas in the respiratory tract under physiological conditions in the human body. When this gas with appropriate temperature and humidity enters the respiratory tract, it reduces irritation to the airway mucosa, maintains the normal function of the airway mucociliary clearance system, and facilitates the expectoration of sputum. The high-flow gas creates turbulence in the nasal cavity, oral cavity, and pharynx, effectively flushing out the anatomical dead space and reducing the carbon dioxide content inhaled by the patient during the next breath, thereby minimizing carbon dioxide rebreathing [7].

3.2. Physiological effects of HFNC on patients with acute exacerbation of COPD

3.2.1. Improvement of oxygenation

HFNC effectively improves the oxygenation function of patients with acute exacerbation of COPD by providing high-flow, precisely concentrated oxygen and generating a positive end-expiratory pressure (PEEP) effect. Jiang

Xiuming et al. treated patients with severe pneumonia complicated by respiratory failure using HFNC [8]. After treatment, the patients' arterial partial pressure of oxygen (PaO_2) increased from (49.56 ± 4.07) mmHg to (78.44 ± 5.12) mmHg, and their oxygen saturation (SaO_2) increased from (82.62 ± 4.83)% to (97.32 ± 1.75)%. The oxygenation index also significantly improved, fully demonstrating the remarkable effect of HFNC in improving oxygenation. The high-flow gas flushes out the dead space, reducing carbon dioxide rebreathing and increasing the oxygen content in the alveoli. The PEEP effect maintains alveolar patency, prevents alveolar collapse, and improves ventilation/perfusion mismatch, enabling more effective diffusion of oxygen from the alveoli into the bloodstream, thereby increasing arterial partial pressure of oxygen and oxygen saturation, lowering the oxygenation index, and reducing the damage caused by hypoxemia to the body [9].

3.2.2. Reduction of respiratory work

Patients in the acute exacerbation stage of Chronic Obstructive Pulmonary Disease (COPD) experience a significant increase in respiratory muscle workload due to increased airway resistance and pulmonary hyperinflation, making them prone to respiratory muscle fatigue. The high-flow gas provided by High-Flow Nasal Cannula (HFNC) can partially meet the patient's inspiratory demand, reducing the patient's spontaneous inspiratory effort and lowering the respiratory rate. Research by Ren Yuanyuan et al. showed that in the observation group treated with HFNC, the post-treatment respiratory rate decreased from (30.97 ± 4.34) breaths/min to (19.51 ± 2.73) breaths/min, significantly lower than that in the control group treated with non-invasive positive pressure ventilation (NIPPV), which had a post-treatment respiratory rate of 21.57 ± 2.80 breaths/min [10]. Meanwhile, after the gas is warmed and humidified, patients do not need to perform additional warming and humidification of the inhaled gas, reducing upper airway resistance and energy consumption during respiration, thereby effectively reducing respiratory work and alleviating respiratory muscle fatigue, which helps improve the patient's respiratory status [11].

3.2.3. Protection of airway mucosa

The gas with appropriate temperature and humidity entering the airway through HFNC can keep the airway mucosa moist, maintain the normal movement of mucociliary, promote the dilution and excretion of sputum, and reduce the risk of airway obstruction caused by thick sputum. Yang Yuhuan found in her study that the incidence of airway-related complications such as nasal bleeding and dry mouth and nose in patients in the HFNC treatment group was only 5.55%, significantly lower than the 22.22% in the NIPPV group, which is closely related to the protective effect of HFNC on the airway mucosa [12]. At the same time, it avoids the stimulation and damage of dry gas to the airway mucosa, protects the integrity of airway epithelial cells, reduces the risk of respiratory infections, and is conducive to maintaining the normal defensive function of the airway.

4. NIPPV

4.1. Working modes and characteristics of NIPPV

NIPPV mainly includes modes such as continuous positive airway pressure ventilation and bilevel positive airway pressure ventilation. In continuous positive airway pressure ventilation mode, the ventilator provides a continuous positive pressure throughout the respiratory cycle to maintain airway patency and prevent airway collapse, suitable for patients with mild respiratory failure and basically normal respiratory drive [13]. The bi-level positive

airway pressure (BiPAP) ventilation mode provides different levels of positive pressure during the inspiratory and expiratory phases, respectively. The higher pressure during inspiration assists the patient in inhaling and increases alveolar ventilation, while the lower pressure during expiration maintains airway patency and improves oxygenation. BiPAP can be individually adjusted based on the patient's respiratory rate, inspiratory time, etc., making it more suitable for patients with moderate to severe respiratory failure.

NIPPV can provide a stable high concentration of oxygen, effectively improving the patient's oxygenation function. Jiang Jingzheng et al. used NIPPV to treat COPD patients, and after treatment, the patients' PaO_2 increased from (48.7 ± 9.8) mmHg to (82.1 ± 10.7) mmHg, significantly improving their oxygenation status [14]. By setting appropriate pressure levels, alveolar ventilation can be increased, promoting carbon dioxide excretion and correcting hypercapnia. Compared with invasive mechanical ventilation, NIPPV avoids the trauma and related complications caused by tracheal intubation or tracheotomy, such as ventilator-associated pneumonia and airway injury, while preserving the patient's swallowing and coughing functions, facilitating independent sputum expectoration and daily communication.

4.2. Mechanism of action of NIPPV in treating acute exacerbation of COPD

In patients with acute exacerbation of COPD, NIPPV effectively corrects hypoventilation and reduces arterial partial pressure of carbon dioxide by increasing alveolar ventilation. In the study by Huang Guodong et al., in the control group treated with NIPPV, the patients' $PaCO_2$ decreased from (75.17 ± 7.47) mmHg to (66.54 ± 6.13) mmHg after treatment, while in the observation group combined with HFNC, the patients' $PaCO_2$ decreased to (60.02 ± 5.25) mmHg, further demonstrating the fundamental role of NIPPV in reducing $PaCO_2$ [15]. The inspiratory pressure can overcome airway resistance, increase tidal volume, and promote carbon dioxide excretion, while the expiratory pressure maintains alveolar patency through the production of positive end-expiratory pressure effect, preventing alveolar collapse during expiration, improving ventilation/perfusion mismatch, and enhancing oxygenation efficiency. NIPPV can also reduce the load on respiratory muscles, allowing fatigued respiratory muscles to rest. By assisting patients in breathing, it reduces the workload of respiratory muscles, decreases their oxygen consumption, and helps alleviate respiratory muscle fatigue and restore their function. In addition, NIPPV can improve patients' breathing patterns, normalize respiratory rates, reduce ineffective ventilation caused by shallow and rapid breathing, and further enhance respiratory efficiency.

5. Comparison of HFNC and NIPPV applications in acute exacerbation of COPD

5.1. Baseline information

To more intuitively compare the efficacy of HFNC and NIPPV, this study conducted baseline data matching and efficacy analysis on two groups of AECOPD patients receiving different respiratory support methods. The general conditions of the two groups of patients are shown in **Table 1** and **2**, with no statistically significant differences ($p > 0.05$) in terms of age, gender, smoking history, and comorbidities, indicating good comparability.

Table 1. Comparison of general conditions between two groups of patients [n(%), $\overline{x} \pm s$]

Group	n	Age	Gender [n (%)]		Smoking status [n (%)]	
			Male	Female	Non-smoker	Smoking history
HNFC Group	15	78.47 ± 11.59	12(80%)	3(20%)	6(40%)	9(60%)
NIPPV Group	15	77.67 ± 7.56	12(80%)	3(20%)	9(60%)	6(40%)
t/χ^2		0.236	0.000		1.200	
p		0.815	1.000		0.273	

Table 2. Comparison of disease between two groups of patients [n(%), $\overline{x} \pm s$]

Group	n	Hypertension [n (%)]		History of endotracheal intubation [n (%)]		Diabetes [n (%)]	
		Yes	No	Yes	No	Yes	No
HNFC Group	15	7(46.67%)	8(53.33%)	1(6.67%)	14(93.33%)	9(60%)	6(40%)
NIPPV Group	15	6(40%)	9(60%)	0	15(100%)	8(53.33%)	7(46.67%)
t/χ^2		0.148		Fisher		0.156	
p		0.700		1.000		0.693	

Notes: 1. $p < 0.05$ indicates a statistically significant difference.
2. The HNFC group refers to the high-flow oxygen therapy group, and the NIPPV group refers to the non-invasive positive pressure ventilation group.
3. The sample sizes of the two groups were obtained through 1:1 random matching from the original data to ensure baseline comparability.
4. Continuous variables were analyzed using the t-test, while categorical variables were analyzed using the χ2 test or Fisher's exact test.

5.2. Comparison of therapeutic effects

This study compared the changes in physiological indicators at different time points before and after treatment between the two groups of patients. As shown in **Table 3**, after 24 hours of treatment, the HFNC group showed statistically significant improvements in respiratory rate, pH value, and SpO_2 ($p < 0.05$), while the NIPPV group only showed a trend of improvement. This indicates that in the early stages of treatment, HFNC may have a faster or more significant effect in improving respiratory distress and oxygenation.

Table 3. Comparison of respiratory rate, pH value, and SpO_2 indicators between two groups of patients after 24 hours of treatment ($\overline{x} \pm s$)

Indicator	Group	n	Before treatment	After 24h Treatment	*t*-value	*p*-value
Respiratory rate (breaths/min)	HFNC group	15	23.47 ± 4.12	21.07 ± 1.94	2.18	0.047
	NIPPV group	15	22.60 ± 4.72	20.27 ± 2.96	1.73	0.106
pH value	HFNC group	15	7.33 ± 0.04	7.37 ± 0.05	-2.42	0.030
	NIPPV group	15	7.34 ± 0.06	7.38 ± 0.07	-1.89	0.080
SpO_2 (%)	HFNC group	15	88.73 ± 6.18	92.47 ± 3.72	-2.24	0.042
	NIPPV group	15	90.07 ± 5.89	91.80 ± 4.36	-0.91	0.379

Notes: 1. $p < 0.05$ indicates a statistically significant difference.
2. This table only analyzes and calculates the indicators with complete data at both the "before treatment" and "one day after treatment" time points in the "General Information" worksheet. Indicators such as PaO2, PaCO2, and $HCO3^-$ were not included in this analysis due to a significant amount of missing data one day after treatment.
3. Paired t-tests were used for comparisons within groups before and after treatment.

To further evaluate the sustainability of the therapeutic effects, we analyzed the data collected three days after treatment. As shown in **Table 4**, the HFNC group maintained statistical advantages in improvements in respiratory rate, pH value, and SpO_2 ($p < 0.05$), while the improvements in all indicators in the NIPPV group did not reach significant levels. This suggests that for the patient population included in this study, HFNC may have a greater advantage in maintaining stable physiological indicators.

Table 4. Comparison of respiratory rate, pH value, and SpO_2 between two groups three days after treatment ($\overline{x} \pm s$)

Indicator	Group	n	Before treatment	After 3 days treatment	*t*-value	*p*-value
Respiratory rate (breaths/min)	HFNC	10	24.20 ± 3.88	21.10 ± 1.91	2.72	0.023*
	NIPPV	10	22.70 ± 5.06	19.60 ± 2.95	2.15	0.059
pH value	HFNC	10	7.32 ± 0.04	7.38 ± 0.05	-3.16	0.011*
	NIPPV	10	7.33 ± 0.07	7.36 ± 0.08	-1.41	0.192
SpO_2 (%)	HFNC	10	89.10 ± 6.55	93.80 ± 3.88	-2.51	0.033*
	NIPPV	10	90.00 ± 6.15	92.70 ± 4.83	-1.57	0.152

Note: 1. $p < 0.05$ indicates a statistically significant difference.
2. This table only analyzes and calculates the indicators with complete data at both the "before treatment" and "three days after treatment" time points in the "General Information" worksheet. Indicators such as PaO2, PaCO2, and $HCO3^-$ were not included in this analysis due to a significant amount of missing data three days after treatment.
3. Paired t-tests were used for comparisons within groups before and after treatment.
4. Continuous variables were analyzed using t-tests, while categorical variables were analyzed using $\chi 2$ tests or Fisher's exact tests.

The ROX index (SpO_2/FiO_2/respiratory rate) is a sensitive indicator for evaluating early responses to respiratory support. The comparison of ROX indices between the two groups of patients two hours after treatment is shown in **Table 5**. Although the average value in the NIPPV group was slightly higher, the difference between groups was not statistically significant ($p > 0.05$), indicating that in the early stages of treatment, the two methods may be equivalent in terms of their comprehensive effects on alleviating respiratory distress in patients.

Table 5. Comparison of ROX index between the two groups after 2 hours of treatment ($\overline{x} \pm s$)

Group	n	ROX index (2 hours post-treatment, $\overline{x} \pm s$)
HFNC Group	15	10.33 ± 3.87
NIPPV Group	15	11.56 ± 2.89

Note: 1. Independent samples t-test was used for inter-group comparison, with $t = -0.99$ and $p = 0.331$. 2. ROX Index = SpO_2 / (FiO_2 × Respiratory rate). The data in this table is directly sourced from the "ROX Index After 2 Hours of Treatment" column in the "General Information" worksheet. 4. Results Explanation: There was no statistically significant difference in the ROX Index between the two groups after 2 hours of treatment ($p = 0.331$).

When treating patients with acute exacerbation of COPD, both HFNC and NIPPV demonstrate certain efficacy in improving oxygenation and ventilation, albeit with differences in various indicators. For oxygenation improvement, HFNC enhances oxygenation through high-flow flushing of the dead space and positive end-expiratory pressure effects, while NIPPV improves oxygenation by setting appropriate pressure levels to maintain

alveolar patency and increase ventilation volume. Multiple studies have shown that in patients with mild to moderate respiratory failure, HFNC and NIPPV exhibit similar initial improvements in the oxygenation index [16]. However, in patients with severe respiratory failure, NIPPV may offer a greater advantage in improving oxygenation due to its ability to provide higher pressure support.

In terms of ventilation improvement, NIPPV directly increases alveolar ventilation volume and significantly reduces arterial partial pressure of carbon dioxide, making it particularly suitable for patients with pronounced hypercapnia [17]. Although HFNC can also reduce carbon dioxide rebreathing by flushing the dead space, its effect on reducing arterial partial pressure of carbon dioxide is relatively weaker. Regarding reintubation rate and mortality, analyses indicate that nasal high-flow oxygen therapy can improve sputum characteristics through warming and humidification, making sputum easier to expectorate and creating favorable conditions for sputum evacuation, thereby reducing the risk of tracheal intubation.

5.3. Comparison of patient tolerance and comfort

HFNC offers significant advantages in terms of patient tolerance and comfort. HFNC utilizes a nasal cannula for connection, causing minimal facial pressure and reducing the occurrence of complications such as skin damage and eye irritation. The warmed and humidified gas better meets the physiological needs of the human body, alleviates discomfort in the patient's respiratory tract, and does not affect the patient's ability to eat, drink, or speak, making it more acceptable to patients. In contrast, NIPPV is connected via a mask, which may cause significant pressure on the patient's face and, when worn for extended periods, can easily lead to skin damage, particularly on the bridge of the nose and cheeks. The study by Sun Panbo et al. revealed that the incidence of adverse reactions such as skin injury and claustrophobia in the conventional group receiving standalone NIV treatment was 34.48%, whereas it was only 10.34% in the intervention group treated with HFNC combined with sequential NIV ($p < 0.05$) [18]. Masks may also obstruct the patient's field of vision and induce claustrophobia, making them intolerable for some patients. Additionally, discomforts such as oropharyngeal dryness and flatulence may occur during NIPPV treatment, further reducing patient comfort and compliance.

5.4. Comparison of complication incidence rates

The incidence of complications with HFNC is relatively low. Due to its minimal intervention in the airway, the primary complications are nasal mucosa dryness and bleeding. However, these complications can be effectively reduced by appropriately adjusting the temperature, humidity, and gas flow. In the study by Shi Lihong et al., the complication incidence rate in the HFNC group was 4.08% (2/49), with only one case of atelectasis and one case of abdominal distension; in contrast, the NIPPV group had a complication incidence rate of 6.38% (3/47), with two cases of infection and one case of abdominal distension [19]. In addition to mask-related complications such as facial skin injury and eye irritation, NIPPV may also cause oropharyngeal dryness, flatulence, aspiration, and other complications. Prolonged use of NIPPV increases water loss in the patient's oropharyngeal region, leading to oropharyngeal dryness; when pressure settings are inappropriate or the patient does not cooperate well, gas may enter the gastrointestinal tract, causing flatulence; when the patient is unconscious or has a weakened cough reflex, there is a risk of aspiration. These complications may affect the patient's treatment outcomes and rehabilitation process.

6. Conclusion

As non-invasive respiratory support methods, HFNC and NIPPV each have distinct characteristics in the treatment of acute exacerbations of COPD. HFNC (High-Flow Nasal Cannula) offers advantages in improving oxygenation, enhancing patient tolerance and comfort, and reducing the incidence of complications, making it particularly suitable for patients with mild to moderate respiratory failure who are intolerant to NIPPV (Non-Invasive Positive Pressure Ventilation). NIPPV, on the other hand, demonstrates significant efficacy in increasing alveolar ventilation and correcting hypercapnia, serving as the preferred option for patients with acute exacerbation of COPD (Chronic Obstructive Pulmonary Disease) complicated by acute hypercapnic respiratory failure. Clinicians should fully consider factors such as the patient's underlying condition, type of respiratory failure, and tolerance to select HFNC, NIPPV, or a combination of both appropriately to achieve the best therapeutic outcomes. Meanwhile, further in-depth research is needed in the future to optimize treatment strategies and improve the management of patients with acute exacerbation of COPD.

Funding

2022 Inner Mongolia Autonomous Region Health and Wellness Science and Technology Program Project (Project No.: 202201533)

Disclosure statement

The authors declare no conflict of interest.

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