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REVIEW

Comparison of High-Flow Nasal Cannula with Conventional Oxygen Therapy in Patients with Hypercapnic Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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Purpose: This study aimed to evaluate the clinical outcomes of high-flow nasal cannula (HFNC) compared with conventional oxygen therapy (COT) in patients with hypercapnic chronic obstructive pulmonary disease (COPD), including arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2), respiratory rate (RR), treatment failure, exacerbation rates, adverse events and comfort evaluation.

Patients and Methods: PubMed, EMBASE and the Cochrane Library were retrieved from inception to September 30, 2022. Eligible trials were randomized controlled trials and crossover studies comparing HFNC and COT in hypercapnic COPD patients. Continuous variables were reported as mean and standard derivation and calculated by weighted mean differences (MD), while dichotomous variables were shown as frequency and proportion and calculated by odds ratio (OR), with the 95% confidence intervals (Cl). Statistical analysis was performed using RevMan 5.4 software.

Results: Eight studies were included, five with acute hypercapnia and three with chronic hypercapnia. In acute hypercapnic COPD, short-term HFNC reduced $PaCO_2$ (MD −1.55, 95% CI: −2.85 to −0.25, $I^2 = 0\%$, $p < 0.05$) and treatment failure (OR 0.54, 95% CI: 0.33 to 0.88, $I^2 = 0\%$, $p<0.05$), but there were no significant differences in PaO_2 (MD −0.36, 95% CI: −2.23 to 1.52, $I^2 = 45\%$, $p=0.71$) and RR (MD −1.07, 95% CI: −2.44 to 0.29, $I^2 = 72\%$, $p=0.12$). In chronic hypercapnic COPD, HFNC may reduce COPD exacerbation rates, but there was no advantage in improving $PaCO_2$ (MD −1.21, 95% CI: −3.81 to 1.39, $I^2 = 0\%$, $p=0.36$) and PaO_2 (MD 2.81, 95% CI: −1.39 to 7.02, $I^2 = 0\%$, $p=0.19$).

Conclusion: Compared with COT, short-term HFNC reduced $PaCO_2$ and the need for escalating respiratory support in acute hypercapnic COPD, whereas long-term HFNC reduced COPD exacerbations rates in chronic hypercapnia. HFNC has great potential for treating hypercapnic COPD.

Keywords: nasal high-flow oxygen therapy, conventional oxygen therapy, hypercapnia, chronic obstructive pulmonary disease, meta-analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide cause of morbidity and mortality with a growing burden.[1] The progression of COPD leads to hypercapnic respiratory failure, which is thought to be associated with exacerbation recurrence, poor disease prognosis, and high mortality.[2] Noninvasive ventilation (NIV) can reduce the partial pressure of carbon dioxide in hypercapnic COPD patients; however discomfort and intolerance limit its widespread application.[3]

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Therefore, conventional oxygen therapy (COT) is still the main method of respiratory support,[4] but the maximum oxygen flow rate it can provide is limited. Previous study has reported a high risk of intubation and invasive mechanical ventilation (IMV) in acute mild acidosis COPD patients treated with COT.[5] In addition, despite improved survival in COPD when treated with long-term oxygen therapy (LTOT), life expectancy is limited when accompanied by comorbidities and hypercapnia.[6] Therefore there is a need to seek alternative strategies.

The high-flow nasal cannula (HFNC) is a new respiratory support technique that provides heated, humidified gas with adjustable oxygen fraction through a special large-bore nasal cannula, with a maximum flow rate of 60 liters per minute (L/min).[7] The main mechanisms of HFNC include creating a low level of positive end-expiratory pressure (PEEP), washing out of nasopharyngeal dead space, decreasing inspiratory effort, and improving airway clearance.[7] In the acute setting, short-term use of HFNC has been found to decrease respiratory rate (RR) and tissue carbon dioxide, and increase tidal volume in COPD patients compared to COT.[8] HFNC has also been shown to reduce inspiratory effort and improve lung volume and compliance in patients with acute hypoxic respiratory failure.[9] A meta-analysis found that HFNC reduced the risk of intubation or escalation of oxygen therapy for acute hypoxemic respiratory failure compared to COT.[10] In the chronic setting, long-term HFNC are thought to enhance pulmonary mucosal cilia function and improve secretion clearance, primarily through humidification.[2] A randomized controlled trial reported that long-term adjunct HFNC therapy reduced exacerbations and hospital readmission in COPD patients with hypoxic failure treated with LTOT.[11]

However, the effect of HFNC on physiological indicators and clinical outcomes in COPD patients with hypercapnia remains uncertain. A previous meta-analysis showed no statistic differences in arterial partial pressure of carbon dioxide ($PaCO_2$) and arterial partial pressure of oxygen (PaO_2) between the HFNC and COT.[12] However, it only included four studies, and only half of patients being hypercapnia. After this, several studies with larger sample sizes were published,[2,4,13,14] but findings were inconsistent. Therefore, we sought to perform a systematic review and meta-analysis, including recent data, to assess the role of HFNC in hypercapnic COPD compared to COT.

Material and Methods

The review protocol was registered at PROSPERO (CRD42022372244) and reported according to the PRISMA guidelines.[15]

Search Strategies

We conducted a systematic search of PubMed, EMBASE and the Cochrane Library from inception to September 30, 2022. A retrospective search was also performed on March 24, 2023. The references of relevant articles were also further reviewed to avoid missing any studies. The comprehensive search strategy included the following Medical Subject Headings (MeSH) terms and keywords: chronic obstructive pulmonary disease, COPD, High Flow Oxygen, High-Flow Nasal Cannula, High-flow nasal oxygen therapy, High-Flow Nasal Cannula Oxygen Therapy, High flow oxygen therapy, and randomized controlled trials. There were no limitations on language. The detailed search strategies are presented in Appendix 1.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Population: The research populations were COPD patients with hypercapnia. (2) Intervention measures: HFNC was used in the experimental group, and COT was used in the control group. (3) Outcomes: $PaCO_2$, PaO_2, RR, treatment failure (defined as meet the criteria for NIV or IMV), exacerbation rates, adverse events, and comfort evaluation. If multiple time points reported, we used the data of 24 hours after randomization for acute patients and longest available for chronic patients. (4) Study design: randomized controlled studies and crossover studies.

Exclusion criteria were as follows: (1) Patients younger than 18 years old. (2) Abstract publications, conference presentations, case reports, editorials or reviews. (3) Studies with incomplete data, which could not be extracted and included for synthesized analysis.

Two investigators independently screened the titles, abstracts, and full texts to determine eligible articles. Any disagreements were resolved by consensus with a third author.

Data Extraction

Two investigators independently extracted the relevant data and information from the eligible studies including authors, publication year, country, study design, sample size, hypercapnia type, interventions, controls, flow rate of HFNC, baseline of PH, $PaCO_2$ and PaO_2, outcomes and follow-up duration. Any disagreements were resolved through discussion or evaluation with a third author.

Quality Assessments

Two independent investigators evaluated the quality of included studies using Cochrane's risk of bias assessment tool,[16] including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of related outcomes assessment, incomplete outcome data, selective reporting bias, and other potential biases. Any disagreement was resolved through discussion or evaluation with a third author.

Statistical Analyses

Data for continuous variables were reported as mean and standard derivation (SD) and calculated by weighted mean differences (MD) with the 95% confidence intervals (CIs), while dichotomous variables were shown as frequency and proportion and calculated by odds ratio (OR) with the 95% CIs. If means and SD were not provided, we were estimated according to methods from Luo and Wan.[17,18] Heterogeneity between studies was evaluated using the χ^2-based Q test and quantified by using the I^2 test, with a significance value of at $P<0.10$ or $I^2 \geq 50\%$ respectively.[19] If there was no significant heterogeneity, a fixed model was used; otherwise, a random model was used. Publication bias assessment and sensitivity analyses was not performed due to the limited number of studies (below 10) included in each analysis. Statistical analysis was performed using RevMan 5.4 software. $P < 0.05$ was considered to be statistically significant.

Results

Selected Studies and Characteristics

We identified 425 studies in our initial literature search, as shown in Figure 1. After duplicate studies (n = 141) and irrelevant topics (n = 244) were removed, forty potentially relevant literature were reserved. Eventually, eight studies were included in our meta-analysis.[2,4,13,14,20–23]

The characteristics of the included studies and patients are shown in Table 1 and Table 2 respectively. A total of 1006 patients were included in our study, of which 488 patients treated with HFNC and 518 patients treated with COT. Five of the studies were of patients with acute hypercapnic COPD receiving HFNC for a short period of time (ranging from 30 minutes to several days),[4,13,14,20,23] while three focused on patients with stable hypercapnia receiving HFNC for a long period of time (ranging from 6 weeks to 12 months).[2,21,22]

Quality Assessment

The results of the quality assessment are shown in Figure 2. All trials were at high risk of performance bias as blinding of patients to treatment assignment was not possible. Since most of the outcome indicators are objective, they would not have a significant impact on outcomes even if the patients were not blinded. With the exception of this field, one study was deemed to have a high risk of bias,[20] and the remaining studies were considered to have a low or unclear risk of bias.

Outcome Analysis

$PaCO_2$

Eight studies compared $PaCO_2$,[2,4,13,14,20–23] five of them concerning patients with acute hypercapnia COPD,[4,13,14,20,23] and three on chronic hypercapnia.[2,21,22] In acute patients, there was no heterogeneity among studies ($I^2 = 0\%$, Q test

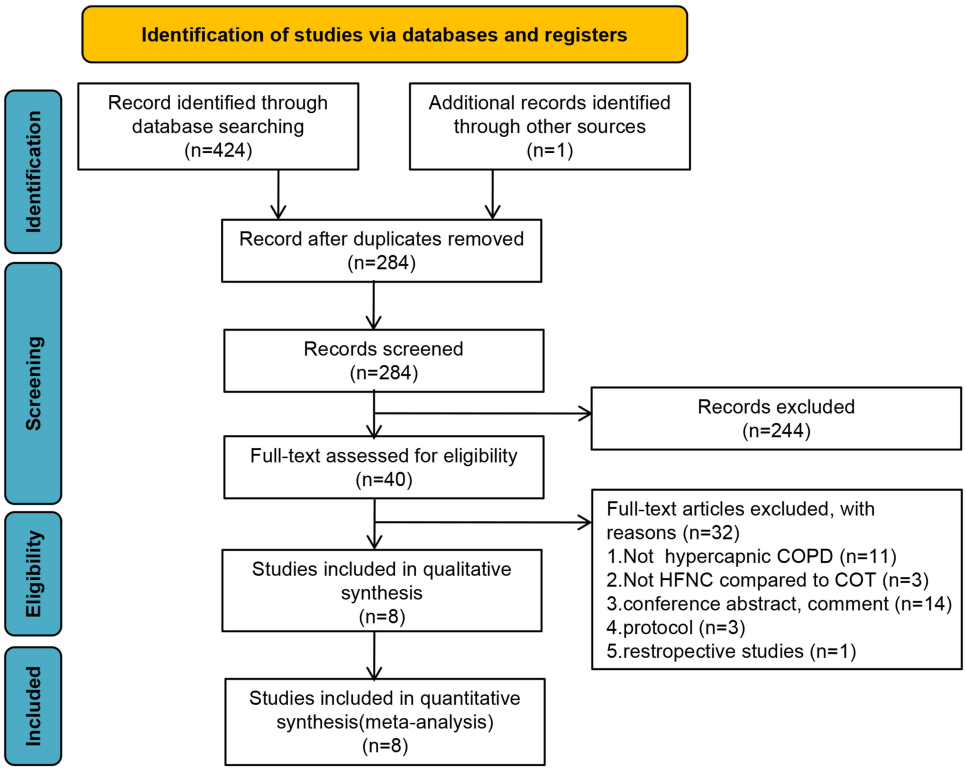

Figure 1 Flow diagram of the study selection.

P=0.49), so the fixed-effect model was used. Compared to COT, $PaCO_2$ was lower in HFNC group (MD −1.55, 95% CI: −2.85 to −0.25, Z = 2.34, p =0.02), as shown in Figure 3A.

In chronic patients, there was no heterogeneity among studies (I^2 = 0%, Q test P=0.96), so the fixed-effect model was used. We observed no significant difference between the two groups in $PaCO_2$ (MD −1.21, 95% CI: −3.81 to 1.39, Z = 0.91, p =0.36), as shown in Figure 3B.

PaO_2

Seven studies compared PaO_2,[2,4,14,20–23] of which four concerning acute hypercapnia COPD patients,[4,14,20,23] and three for chronic patients.[2,21,22] In acute patients, there was no heterogeneity between the studies (I^2 = 45%, Q test P=0.14), so the fixed-effect model was used. Meta-analysis showed no statistical difference between HFNC and COT in terms of improvement in PaO_2 (MD −0.36, 95% CI: −2.23 to 1.52, Z = 0.37, p=0.71), as shown in Figure 4A.

In chronic patients, there was no heterogeneity between the studies (I^2 = 0%, Q test P=0.51). Similarly, fixed-effects models showed no differences in PaO_2 between the two groups (MD 2.81 95% CI: −1.39 to 7.02, Z =1.31, p=0.19), as shown in Figure 4B.

RR

Four studies about acute hypercapnia compared the RR.[4,13,14,20] There was heterogeneity (I^2 = 72%, Q test P=0.01), so the random effect model was used. Meta-analysis showed no statistical difference between the two groups (MD −1.07, 95% CI: −2.44 to 0.29, Z = 1.54, p=0.12), as shown in Figure 5.

Treatment Failure

Two studies about acute hypercapnic COPD reported data on treatment failure.[4,14] To obtain an accurate number of patients who met the criteria for escalation of ventilation, we excluded patients who received NIV due to intolerance. There was no heterogeneity (I^2 = 0%, Q test P=0.48), so the fixed effect model was used. The pooled results showed

Table 1 Characteristic of Included Studies

Study	Country	Study Design	HFNC Group	COT Group	Adjusted FiO_2	HFNC Flow Rate	HFNC Duration	Follow-Up Duration	Endpoints
Di Mussi 2018[20]	Italy	Single-center, self-cross control study	HFNC	COT	SaO_2 90–93%	20–60L/min	30 min	1 h	①②③
Li 2020[4]	China	Multi-center, randomized trial	HFNC	COT	SpO_2 90–93%	33.4 ± 5.6 L/min	> 15 h per day	3 months	①②③④⑦
Longhini 2019[13]	Australia	Multi-center, randomized crossover study	HFNC	Standard oxygen	SpO_2 90–94%	50 L/min	30 min	150 min	①③⑦
Nagata 2018[21]	Japan	Multi-center, randomized crossover trial	HFNC plus LTOT	LTOT	SpO_2 > 88%	20–40L/min	6 weeks (> 4 h per night)	12 weeks	①②⑥
Nagata 2022[2]	Japan	Multi-center, randomized trial	HFNC plus LTOT	LTOT	SpO_2 > 88%	20–40L/min	52 weeks (> 4 h per night)	52 weeks	①②⑤⑥
Storgaard 2020[22]	Denmark	Multi-center, post- hoc analysis of randomized trial	HFNC plus LTOT	LTOT	SpO_2 > 88%	15–60 L/min	Average 6.9 h per day, preferably at night	12 months	①②⑤
Xia 2022[14]	China	Multi-center, randomized trial	HFNC	COT	SpO_2 90–95%	20–60L/min, median 30 L/min	As long as possible per day	90 days	①②③④⑥⑦
Yang 2019[23]	China	Single-center, randomized trial	HFNC	COT	NA	Starting at 40 L/min	NA	48 h	①②

Notes: Endpoints: ①arterial partial pressure of carbon dioxide (PaCO2); ②arterial partial pressure of oxygen (PaO2); ③respiratory rate; ④treatment failure, ⑤exacerbation rates; ⑥adverse events; ⑦patient comfort.
Abbreviations: HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; LTOT, long-term oxygen therapy; FiO_2, fraction of inspired oxygen; SpO2, pulse oxygen saturation; SaO_2, arterial oxygen saturation; NA, not applicable.

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Table 2 Characteristics of Patients in the Included Studies

Study	Type	Group	Sample Size (n)	Age (Years)	Gender (M/F)	Baseline PH (Units)	Baseline $PaCO_2$ (mmHg)	Baseline PaO_2 (mmHg)
Di Mussi 2019[20]	Acute	HFNC	14	71.5±9.0	12/2	NA	NA	NA
		COT	14	71.5±9.0	12/2	NA	NA	NA
Li 2020[4]	Acute	HFNC	160	68.4±7.7	101/59	7.38±0.03	54.9±7.1	54.7±5.2
		COT	160	68.3±6.9	106/54	7.39±0.04	54.2±6.0	54.9±4.9
Longhini 2019[13]	Acute	HFNC	30	72.5±8.2	17/13	7.40(7.37–7.44)	54.8(46.9–65.0)	NA
		COT	30	72.5±8.2	17/13	7.39(7.37–7.43)	54.1(47.1–66.4)	NA
Nagata 2018[21]	Chronic	HFNC	13	73.8±6.9	12/1	7.39±0.03	51.5±8.2	89.2±27.3
		COT	16	76.2±9.3	14/2	7.39±0.03	52.3±6.7	87.8±38.0
Nagata 2022[2]	Chronic	HFNC	49	73.0±7.4	44/5	7.38±0.02	51.4±5.0	80.37±21.75
		COT	50	75.2±6.7	44/6	7.39±0.02	50.5±5.0	84.1±21.85
Storgaard 2020[22]	Chronic	HFNC	31	67.0±NA	10/21	7.39±0.03	54.7±9.0	73.5±11.25
		COT	43	68.0±NA	13/30	7.40±0.03	54.0±4.5	75.0±12
Xia 2022[14]	Acute	HFNC	158	70.0(65.0–75.0)	140/18	7.40(7.37–7.42)	50.4(47.3–56.3)	70.4(57.0–83.0)
		COT	172	69.0(63.5–74.5)	137/35	7.40(7.37–7.43)	51.7(47.6–58.0)	68.0(56.0–83.7)
Yang 2019[23]	Acute	HFNC	35	66.3± 8.8	23/12	NA	NA	NA
		COT	37	65.9±10.9	22/15	NA	NA	NA

Note: Data are presented as mean ± standard deviation or median (interquartile range).
Abbreviations: HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; PH, potential of hydrogen; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; NA, not applicable.

a lower rate of treatment failure in the HFNC group (OR 0.54, 95% CI: 0.33 to 0.88, Z = 2.48, p<0.05), as shown in Figure 6A.

We also combined the results of the actual upgraded to NIV and found a lower proportion of patients in the HFNC group (OR 0.57, 95% CI: 0.35 to 0.94, Z = 2.23, p<0.05), as shown in Figure 6B. However, pooled analysis for IMV was not allowed due to the fact that only one study had patients experienced IMV and the number was too small,[14] but the results showed no difference between the two groups (4/158 for HFNC group, 1/172 for COT group, p=0.198).

Exacerbation Rates

Two studies about chronic hypercapnic COPD compared exacerbation rates over one year.[2,22] We were unable to pool the results because of different assessment methods. Storgaard reported that long-term HFNC stabilized the exacerbation rate, but COT did not.[22] Specifically, compared with the year prestudy, the exacerbation rate for the control group increased by 2.2/year (P<0.001), while the HFNC group remained essentially stable with an increase of 0.15/year

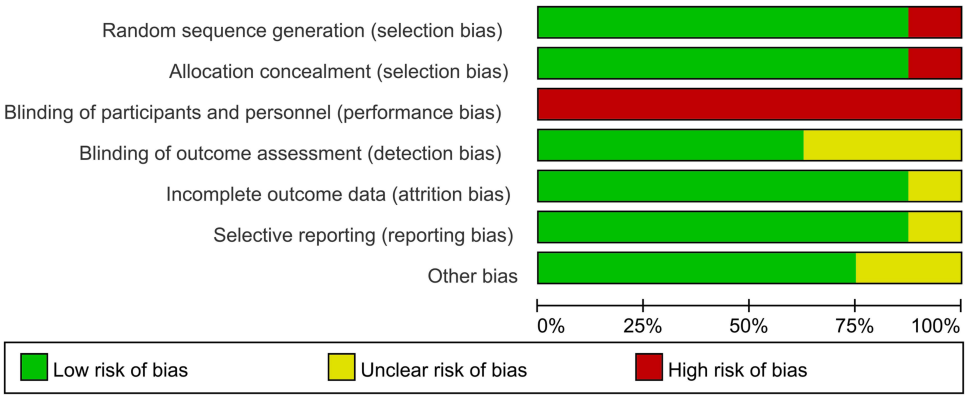

Figure 2 Quality assessment of bias graph.

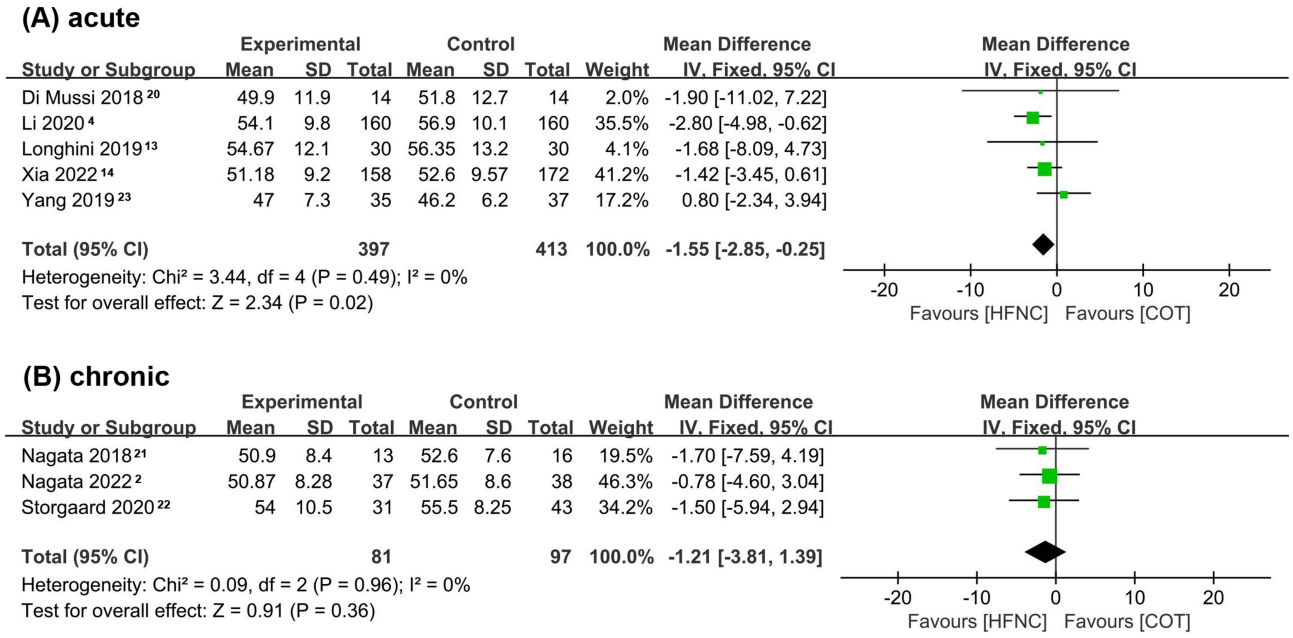

Figure 3 Forest plot of PaCO2, (**A**) acute hypercapnia, (**B**) chronic hypercapnia.

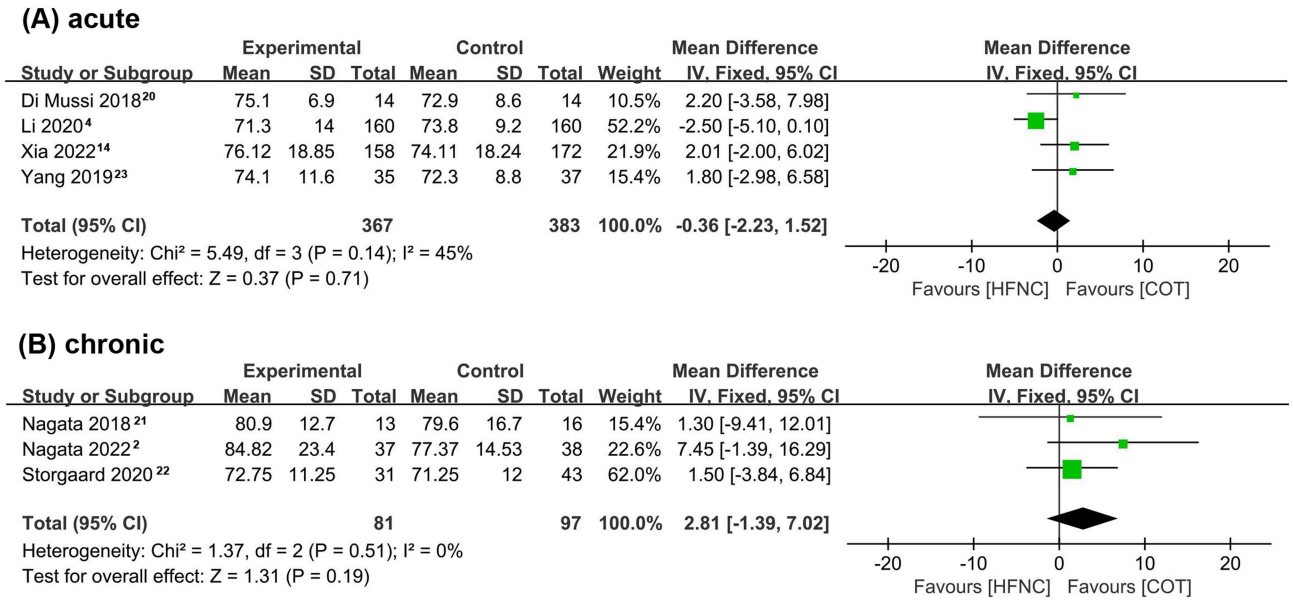

Figure 4 Forest plot of PaO2, (**A**) acute hypercapnia, (**B**) chronic hypercapnia.

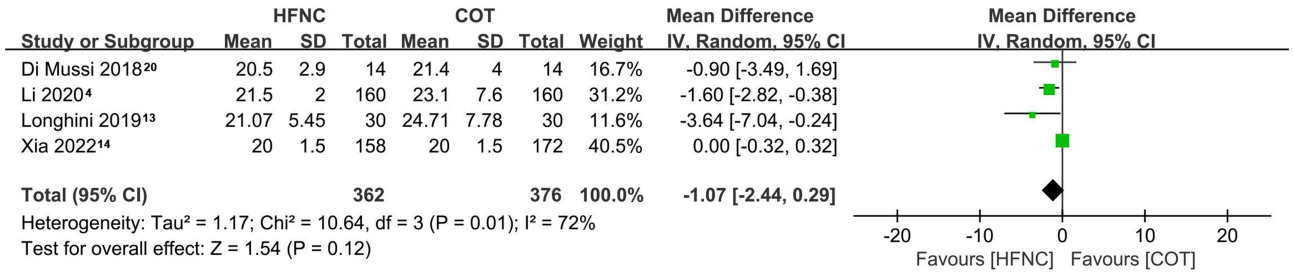

Figure 5 Forest plot of respiratory rate.

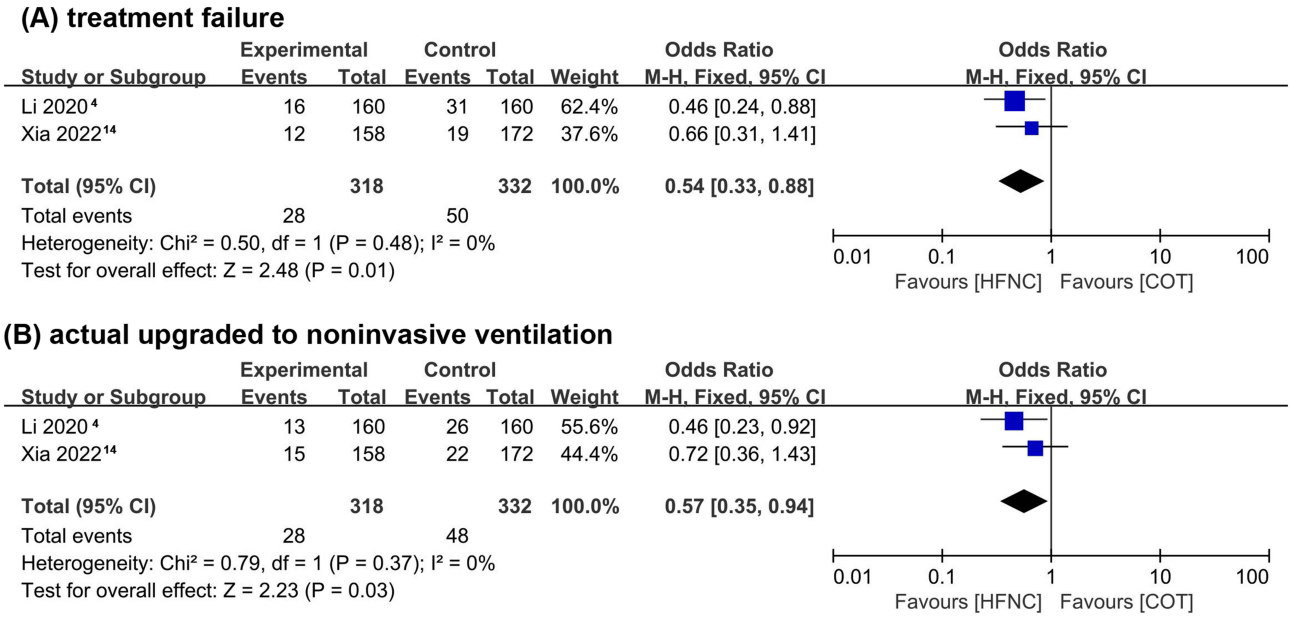

Figure 6 Forest plot of treatment failure in acute hypercapnia, (**A**) Treatment failure, (**B**) Actual upgraded to noninvasive ventilation.

(p=0.661). Nagata's study also showed that domiciliary HFNC can reduce moderate/severe COPD exacerbations,[2] the adjusted ratios (95% CIs) of the mean exacerbation count in the COT group compared with that in the HFNC group was 2.85 (95% CIs 1.48–5.47, P =0.002).

Adverse Events

Three studies compared adverse events with insufficiently reported data,[2,14,21] so we could only provide a description of their occurrence. In the studies by Xia and Nagata,[14,21] no severe adverse events attributable to the randomized group occurred. In the study by Nagata,[2] the most common adverse events in the HFNC/LTOT and LTOT groups were respiratory, thoracic, and mediastinal disorders (38.8% versus 42.0%), with no significant difference in the incidence between the two groups. Also, the overall incidence of severe adverse events was similar between the two groups (38.8% versus 32.0%).

Patient Comfort

Three studies compared comfort using different indicators.[4,13,14] Two of the studies reported better comfort in the HFNC group,[4,13] while one study found no difference between the two groups.[14] The results from trials were summarized in Table S1.

Discussion

This systematic review and meta-analysis included eight studies to examine whether there were differences between HFNC therapy and COT in the treatment of hypercapnic COPD. In acute hypercapnic COPD, short-term HFNC reduced carbon dioxide retention and the need for higher respiratory support, but there were no significant differences in PaO_2 and RR. In chronic hypercapnic COPD, HFNC may reduce COPD exacerbation rates, but there was no advantage in improving $PaCO_2$ and PaO_2.

A previous meta-analysis by Huang[12] included four original studies and found no significant difference in $PaCO_2$ reduction and PaO_2 improvement between the HFNC and COT. Compared to it, our review focused on patients with hypercapnic COPD, included more studies and patients, evaluated more outcome indicators, and obtained different results.

Our study found that the effect of HFNC on $PaCO_2$ was related to the duration of hypercapnia and the HFNC treatment period. In acute patients, short-term HFNC was more effective in reducing $PaCO_2$ than COT. In fact, several randomized clinical studies have shown that the ability of HFNC to maintain $PaCO_2$ was comparable to NIV in

exacerbated COPD.[24] Physiological studies have shown that HFNC can flush the upper airway and reduce anatomical dead space with the assistance of a positive airway pressure effect, allowing higher ventilation per minute to facilitate gas exchange.[25] At the same time, HFNC also decreased inspiratory resistance and room air dilution effect by providing gas flow matching or higher than the peak inspiratory flow.[25] Furthermore, HFNC could decrease neuroventilatory drive and work of breathing in COPD patients and alleviate muscle fatigue.[20]

However, in chronic patients, there was no significant difference in $PaCO_2$ between long-term HFNC groups and COT groups. Persistent carbon dioxide retention leads to poor response of respiratory central chemoreceptors to carbon dioxide and patients become dependent on hypoxic drive, so a decrease in PaO_2 may stimulate respiratory drive and reduce $PaCO_2$.[22] In the chronic hypercapnia studies we included, there was a tendency for PaO_2 to decrease more in the COT group, which may be one of the explanatory mechanisms. Moreover, long-term follow-up may have reduced patient compliance and introduced other confounding factors, such as differences in prescribed medications and pulmonary rehabilitation. In fact, Nagata[21] reported that when statistically controlling the time effect and allocation effect, the adjusted results showed lower $PaCO_2$ in HFNC groups.

Our analysis found no statistical difference in PaO_2 between the two groups, which requires further research. Sztrymf's research has demonstrated the efficiency of HFNC in ameliorating oxygenation in patients with acute respiratory failure.[26] Proper management of fraction of inspired oxygen (FiO_2) and PEEP is the key to maintain adequate oxygenation.[27] The HFNC is capable of providing high gas flow rates, creating a certain amount of PEEP, and providing more stable FiO_2 than low-flow oxygen delivery.[27] Theoretically, it has an advantage over COT in terms of improving oxygenation. However, our pooled results in patients with acute hypercapnic COPD did not support this, probably for the following reasons. First, since the cannula is part of an open system, pharyngeal pressure is limited. Airway pressure increased as flow increased,[27] but pressure remained below 3 cmH_2O even at 60 L/min flow,[28] which is far from adequate for comparison with NIV. In our included clinical studies, most patients received oxygen flow rates significantly lower than 60 L/min,[4,13,14,23] so HFNC produced an even lower PEEP. Moreover, FiO_2 was dynamically adjusted with oxygenation in our included studies, and both patients with different oxygen therapy could be maintained to arterial oxygen saturation (SaO_2) or pulse oxygen saturation (SpO_2) levels by adjusting FiO_2.[4,13,14,20] Although PaO_2 levels were comparable in both groups after treatment, there was no hypoxic respiratory failure in either group, indicating the potential benefit of HFNC in improving oxygenation.

In patients with chronic hypercapnia, our pooled results showed that the ability of HFNC to stabilize PaO_2 is comparable to COT. There may be other explanations than the above mechanism. COPD patients have persistent inflammatory reactions in the airways, pulmonary parenchyma and pulmonary vessels, resulting in repeated airway remodeling, parenchymal destruction and pulmonary vessels abnormalities that contribute to a decrease in pulmonary gas exchange ability.[29] These histopathological changes accumulate over the long-term duration of the disease and are difficult to reverse with HFNC treatment. Furthermore, the three included studies were designed to use HFNC mainly at night,[2,21,22] but blood gas measurements were mostly evaluated in the daytime,[2,21] several hours after HFNC cessation, which may lead to an underestimation of improvement in physiological parameters.

Similarly, RR was comparable between the two groups. Previous studies have found that HFNC can significantly reduce RR compared with COT in patients with dyspnea or acute respiratory failure,[30,31] but the baseline RR in these studies was rapid, reaching 32–33.4 breaths/min compared to 21 breaths/min in our study. The mechanism is likely to be a reduction in anatomical dead space with HFNC, which resulting in improved ventilation and perfusion matching.[32] However, given the high heterogeneity of pooled results, we need to be cautious and more original studies were required.

The need for treatment escalation is the main indicator to evaluate the treatment outcome of acute hypercapnic COPD patients. Our study found that HFNC reduced the need for escalated respiratory support, which is consistent with the study by Rochwerg[10] in patients with acute hypoxic respiratory failure. The physiological mechanisms of HFNC may underlie its clinical benefit. Increased HFNC flow rate gradually may reduce inspiratory effort and minute ventilation; improve pulmonary ventilation, dynamic compliance, and oxygenation,[33] thus decreasing the rates of intubation or NIV secondary to hypoxia. In addition, HFNC decreased the risk of self-inflicted lung injury by more fully matching the patient's respiratory flow requirements.[10] However, it is noteworthy that in the study by Xia,[14] the length of hospital stay and hospital costs were significantly higher in the HFNC group than those in the COT group, which they suggest may be

related to the delayed escalation of NIV in HFNC group. Therefore, we recommend that HFNC should be fully evaluated by experienced clinicians and that treatment strategies should be adjusted in time for patients who fail to improve with HFNC treatment.

Exacerbation rates were the main indicator to evaluate the treatment outcome of stable hypercapnic COPD patients. Our study found that long-term HFNC reduces exacerbations rate in patients with hypercapnic COPD. Previous studies have indicated that exacerbation history is the most important determinant of frequent exacerbations of COPD and is associated with increased severity.[34] Therefore, it is of great importance to reduce acute exacerbations of COPD. In COPD chronic care, HFNC improves mucociliary function and promotes secretion clearance by providing heated and humidified gas, which will prevent the occurrence of atelectasis and improve the ventilation-perfusion ratio.[27] Also the humidified gas can reduce the chronic airway inflammatory response caused by mucosal dryness.[27] Besides, HFNC can relieve ventilator fatigue,[20,35] and has a have long-term effects promoting respiratory muscle recovery.[35] The above mechanisms may explain the reduction of COPD exacerbation by HFNC, but further mechanistic studies are still needed.

Our meta-analysis has several limitations. First, due to the nature of the interventions applied, blinding of patients was not possible, so all studies were at high risk of performance bias, but all the outcome indicators we assessed were objective except for comfort. Second, the timing and duration of HFNC treatment, as well as the length of follow-up, varied between studies. Third, the number of included studies was too small and included crossover studies. We performed a retrospective search on March 24, 2023, no updated articles were found, but several registered or ongoing clinical trials were noted (NCT05497986, NCT04640948, and NCT04840706). Fourth, there was a lack of sufficient data to perform relevant subgroup analyses to identify specific beneficiaries of HFNC use. Fifth, the medical cost is an important factor influencing clinical application, but only one article reported the cost of treatment, and later studies should focus on the issue of cost.

Conclusions

Our systematic review and meta-analysis suggests that compared with COT, short-term HFNC reduced $PaCO_2$ and the need for escalating respiratory support in acute hypercapnic COPD, whereas long-term HFNC reduced COPD exacerbations rates in chronic hypercapnia. HFNC has great potential for treating hypercapnic COPD. Further large-scale studies are needed to confirm our results and identify specific beneficiaries of HFNC.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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