Acta Med. Okayama, 2024
Vol. 78, No. 3, pp. 271–279

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Effect of Humidified High-Flow Nasal Cannula Oxygen Therapy with a Pulmonary Infection Control Window as a Ventilation Switching Indication in Combination with Atomizing Inhalation of Terbutaline on the Lung Function of Patients with Acute Exacerbation of COPD

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We investigated how humidified high-flow nasal cannula oxygen therapy (HFNC) with a pulmonary infection control (PIC) window as a ventilation switching indication in combination with atomizing inhalation of terbutaline affects the lung function of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). We examined 140 hospitalized AECOPD patients randomized to control and observation groups. Conventional supportive therapy and invasive mechanical ventilation with tracheal intubation were conducted in both groups, with a PIC window as the indication for ventilation switching. Noninvasive positive pressure ventilation (NIPPV) plus atomizing inhalation of terbutaline was used in the control group. In the observation group, HFNC combined with atomizing inhalation of terbutaline was used. Compared to the control group, after 48-hr treatment and treatment completion, the observation group had significantly increased levels of lung function indicators (maximal voluntary ventilation [MVV] plus forced vital capacity [FVC], $p < 0.05$) and oxygen metabolism indicators (arterial oxygen partial pressure [PaO_2], arterial oxygen content [CaO_2], and oxygenation index, $p < 0.05$). The comparison of the groups revealed that the levels of airway remodeling indicators (matrix metalloproteinase-2 [MMP-2], tissue inhibitor of metalloproteinase 2 [TIMP-2] plus MMP-9) and inflammatory indicators (interferon gamma [IFN-γ] together with interleukin-17 [IL-17], IL-10 and IL-4) were significantly lower after 48 h of treatment as well as after treatment completion (both $p < 0.05$). These results demonstrate that HFNC with a PIC window as the indication for ventilation switching combined with atomizing inhalation of terbutaline can relieve the disorder of oxygen metabolism and correct airway hyper-reactivity.

Key words: chronic obstructive pulmonary disease, inhalation, oxygen therapy, pulmonary function, ventilation

Chronic obstructive pulmonary disease (COPD), a progressive disease of incompletely reversible airflow limitation, is characterized by a long disease course and disease relapse in most cases. Patients with COPD often experience decreased lung tissue elasticity, altered lung compliance, and other pathological changes. Their symptoms may take a sharp turn for the worse due to the stimulation of various factors, and acute exacerbation may lead to an increased risk of mortality [1]. Regarding acute exacerbation of COPD (AECOPD), invasive mechanical ventilation is usually applied as the ventilation mode, as it can relieve ventilation disorder and restore patients' oxygenation. Although

Received November 1, 2023; accepted February 29, 2024.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

it relieves clinical symptoms, long-term invasive mechanical ventilation can lead to complications of various severities such as subcutaneous emphysema and ventilator-associated lung infection, thus preventing a rapid recovery and thereby increasing the risk of death [2].

To avoid the occurrence of adverse events due to long-term invasive mechanical ventilation, it is of great significance to switch the ventilation mode. The identification of the right time to switch the ventilation mode is the key to improving the therapeutic effect of long-term ventilation. The patient's comfort level during oxygen inhalation is an indicator that must be considered during ventilation therapy [3]. Noninvasive positive pressure ventilation (NIPPV) is not humidified and thus easily leads to respiratory dryness, difficulty in sputum aspiration, and reduced patient tolerance, and re-intubation is therefore often required. Humidified high-flow nasal cannula oxygen therapy (HFNC) can make up for the deficiency of NIPPV, with confirmed feasibility as well as safety in the treatment of COPD [4, 5].

The optimal guidance time for ventilation therapy remains a controversial issue. The acute exacerbation of the COPD of approx. 80-90% of individuals with COPD is caused by a bronchial-pulmonary infection, which can be effectively controlled by antibacterial treatment [6]. The pulmonary infection control (PIC) window has thus been used as an indication for switching the ventilation mode [7], and this has been validated in different populations with various disease severities [8]. The β_2 adrenergic receptor agonist and bronchodilator terbutaline is capable of relaxing airway smooth muscle, reducing airway resistance, and inhibiting the release of inflammatory factors, and its atomizing inhalation exerts a satisfactory therapeutic effect on COPD [9].

We conducted the present study to assess the therapeutic effect of HFNC with a PIC window as the indication for ventilation switching combined with atomizing inhalation of terbutaline on AECOPD, aiming to obtain clinical evidence for future treatments.

Subjects and Methods

Enrollment of subjects. We enrolled 140 patients with AECOPD who were hospitalized during the period from January 2019 through January 2023, and we applied a random number table to randomly assign the patients to an observation group (n = 70) and a control group (n = 70). The inclusion criteria were as follows: (*i*) patients meeting the standards for the diagnosis of AECOPD in the Chinese Expert Consensus on Diagnosis and Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (2023 revision) issued by the Diagnosis and Treatment Expert Panel for Acute Exacerbation of Chronic Obstructive Pulmonary Disease, *i.e.*, patients who had an acute onset and symptoms such as anhelation aggravation, dyspnea, severe cough, increased sputum quantity, and fever in the short term, as well as manifestations of acute respiratory failure, and (*ii*) not receiving treatment at the disease onset.

The exclusion criteria were patients (*i*) intolerant to HFNC, (*ii*) unable to receive mechanical ventilation or HFNC due to recent upper respiratory tract surgery, (*iii*) a previous tracheal intubation or tracheotomy, (*iv*) not meeting the criteria for a PIC window for mechanical ventilation via a trachea incision, (*v*) end-stage respiratory failure, (*vi*) severe cardiac dysfunction, (*vii*) a malignant tumor, or (*viii*) unmanageable internal medical disease such as hypertension and diabetes.

This study was approved by our hospital's Ethics Committee and was conducted in accord with the principles of the Declaration of Helsinki. Written informed consent for study participation was obtained from all of the patients or their family members.

Conventional supportive treatment. Symptomatic support therapy was applied to both groups of patients for the relief of cough and the elimination of phlegm, along with nutritional support.

Criteria for the PIC window. In addition to conventional supportive treatment, invasive mechanical ventilation with tracheal intubation (*i.e.*, pressure support ventilation [PSV] or synchronized intermittent mandatory ventilation [SIMV] plus other modes) was conducted for the patients in both groups. The indication for ventilation switching was the detection of a PIC window in the patient. The criteria for a PIC window were as follows: (*i*) the bronchial-pulmonary infection shadow was obviously absorbed, (*ii*) the sputum quantity was decreased and the sputum color was lighter, and (*iii*) the patient's body temperature had declined to 38°C or the white blood cell count declined to $\geq 2 \times 10^9$/L or $\leq 10 \times 10^9$/L.

Treatment methods for the control group. NIPPV with a PIC window as the indication for ventilation switching combined with atomizing inhalation of terbutaline was used for the control group. For the NIPPV,

oxygen was supplied by a noninvasive ventilation mask (Philips Healthcare, Cleveland, OH, USA) in the mode of continuous positive airway pressure (CPAP) with the following settings: expiratory pressure 4-5 cmH_2O, inspiratory pressure 10-12 cmH_2O, inspiratory-expiratory ratio 1 : 1.5-1 : 2, fraction of inspiration O_2 (FiO_2) 30-50%, and percutaneous arterial oxygen saturation (SpO_2) 92-98%. These settings were adjusted based on the patient's blood gas results and tolerance during treatment. The treatment lasted for ≥ 48 h, and the ventilation mask was gradually withdrawn according to the specific conditions of the patient. Based on the NIPPV result, the patient inhaled terbutaline (Sichuan Purity Pharmaceutical Co., Sichuan, China) by atomization; in brief, 25 mg of terbutaline was added to the medicine tank and was inhaled by the patient with oxygen as the driving force at a rate of 6 L/min, twice a day (15 min/time) for 7 consecutive days.

Treatment methods for the observation group. HFNC with a PIC window as the indication for ventilation switching combined with atomizing inhalation of terbutaline was administered to the observation-group patients. Specifically, a humidified high-flow oxygen therapy instrument (Fisher & Paykel, New Zealand) was used for oxygen inhalation with the following settings: initial value of oxygen flow 40-50 L/min, FiO_2 30-50%, and SpO_2 92-98%. These settings were adjusted based on the patient's blood gas results and tolerance during treatment. The treatment lasted for ≥ 48 h, and the instrument was gradually withdrawn according to the specific conditions of the patient. Based on the result of the HFNC, an atomizing inhalation of terbutaline was administered for 7 consecutive days as described for the control group.

Pulmonary function evaluation. Prior to treatment as well as after the 48-h treatment and the completion of treatment, the measurement of each patient's maximum voluntary ventilation (MVV) and forced expiratory volume in one second (FEV_1) together with forced vital capacity (FVC) was conducted.

Assessment of oxygen metabolism levels. The levels of arterial oxygen partial pressure (PaO_2), arterial oxygen content (CaO_2), and the oxygenation index (PaO_2/FiO_2) were identified with a blood gas analyzer (Beckman Coulter, Indianapolis, IN, USA) prior to treatment, as well as after the 48-h treatment and treatment completion.

Evaluation of airway hyperreactivity. In each patient's case, the inspiratory pressure (reference range ≤ 20 cmH_2O), peak airway pressure (reference range 10-40 cmH_2O), plateau pressure (reference range 5-13 cmH_2O), and dynamic lung compliance (Cdyn) were recorded by a breathing machine prior to treatment and after the 48-h treatment and treatment completion. Cdyn = tidal volume/(highest airway pressure-end expiratory pressure).

Measurement of airway remodeling and inflammatory indicators. Venous blood (5 mL) was collected before each patient's treatment as well as after the 48-h treatment and completion of treatment and then centrifuged at 3,000 g to separate the upper serum. A Varioskan LUX automatic microplate reader (Thermo Fisher Scientific, Waltham, MA, USA) was used to determine the levels of airway remodeling indicators, *i.e.*, matrix metalloproteinase-2 (MMP-2), MMP-9, and tissue inhibitor of metalloproteinase-2 (TIMP-2) and inflammatory indicators, *i.e.*, interleukin-4 (IL-4), IL-7, and interferon gamma (IFN-γ). All related assay kits were purchased from Unilever Life Sciences Co. (London).

Assessment of treatment outcomes. The efficacy of the treatment was evaluated based on the patients' clinical symptoms and FEV_1 values based on the following: receding clinical symptoms combined with FEV_1 increased by 25-34% was considered 'markedly effective'; an FEV_1 increase by 15-35% along with significant amelioration of clinical symptoms was considered 'effective'; and no improvement or the presence of aggravation was considered 'ineffective'. The efficacy formula was as follows: (markedly effective + effective)/total cases × 100% = the total response rate.

The patients' short-term prognoses. The patients were followed up for 28 days after the completion of their treatment, and the 28-day re-intubation rate was recorded.

Statistical analysis. The statistical analyses and processing of the results were accomplished with SPSS 25.0 software. The measurement data are presented as the mean ± standard deviation (SD) and were compared between the two patient groups with independent-sample *t*-tests. Multiple time points were set for the comparison of repeated measures data that were subjected to a repeated measures analysis of variance (ANOVA). Enumeration data are presented as frequencies and percentages, with the χ^2-test conducted for intergroup comparisons. Probability (p)-values < 0.05 were accepted as significant.

Results

General data. The control group was comprised of 31 females and 39 males aged 49-67 years old (55.64 ± 5.48 years). The observation group was 35 females and 35 males aged 50-68 years old (56.03 ± 5.89 yrs). As shown in Table 1, the patient age, frequency of acute exacerbation, body mass index, gender, course of COPD, and time from the onset of acute exacerbation to treatment were not significantly different between the groups.

Lung function. Prior to treatment, the levels of the lung function indicators FEV_1, MVV, and FVC were not significantly different between the control and observation groups, but they each rose in both groups with the 48-h treatment and after the completion of treatment, at which time the observation group had significantly higher levels compared to the control group ($p < 0.05$) (Table 2).

Oxygen metabolism levels. As shown in Table 3, the oxygen metabolism indicators PaO_2, CaO_2, and the oxygenation index showed no significant between-group differences before the treatment. After the 48-h treatment and at treatment completion, each of the groups had elevated levels of these indicators, and the observation group's levels were significantly higher than those of the control group ($p < 0.05$).

Airway hyper-reactivity parameters. Prior to treatment, there were no significant between-group differences in the airway hyper-reactivity indicators inspiratory pressure, peak airway pressure, plateau pressure, and Cdyn (Table 4). Following the 48-h treatment and at treatment completion, the inspiratory pressure, peak airway pressure, and plateau pressure dropped in both groups, and the observation group exhibited significantly reduced levels compared to the control group ($p < 0.05$). Both patient groups experienced a Cdyn increase, and the increase was significantly higher in the observation group compared to the control group ($p < 0.05$)(Table 4).

Airway remodeling indicators. Before treatment, the between-group differences in the airway remodeling indicators MMP-2, TIMP-2, and MMP-9 were not significant ($p > 0.05$). With the treatment and at treatment completion, these indicators declined in both groups, with significantly lower levels in observation group ($p < 0.05$) (Table 5).

Table 1 The general data of the patients with acute exacerbation of chronic obstructive pulmonary disease

General data	Control group (n = 70)	Observation group (n = 70)	*t*	*P*-value
Gender (male/female)	39/31	35/35	0.459	0.498
Average age (year)	55.64 ± 5.48	56.03 ± 5.89	0.406	0.686
Body mass index (kg/m^2)	23.43 ± 2.65	23.46 ± 2.51	0.069	0.945
Course of chronic obstructive pulmonary disease (year)	4.65 ± 0.78	4.68 ± 0.87	0.215	0.830
Frequency of acute exacerbation (times/year)	2.02 ± 0.29	2.10 ± 0.21	1.869	0.064
Time from the onset of acute exacerbation to treatment (d)	2.46 ± 0.31	2.43 ± 0.28	0.601	0.549

Table 2 The patients' lung function

Indicator	Time point for observation	Control group (n = 70)	Observation group (n = 70)	*t*	*P*-value
FEV_1 (L)	Before treatment	1.34 ± 0.17	1.35 ± 0.19	0.328	0.743
	Following treatment for 48 h	1.78 ± 0.13[a]	2.02 ± 0.15[a]	10.120	< 0.001
	After treatment completion	2.10 ± 0.19[ab]	2.46 ± 0.23[abc]	10.100	< 0.001
MVV (%)	Before treatment	50.43 ± 5.46	50.62 ± 5.38	0.207	0.836
	Following treatment for 48 h	53.42 ± 6.57[a]	57.89 ± 5.92[a]	4.229	< 0.001
	After treatment completion	56.57 ± 6.98[ab]	60.43 ± 8.94[abc]	2.847	0.005
FVC (L)	Before treatment	1.54 ± 0.23	1.55 ± 0.23	0.257	0.797
	Following treatment for 48 h	1.90 ± 0.17[a]	2.13 ± 0.18[a]	7.772	< 0.001
	After treatment completion	2.20 ± 0.18[ab]	2.79 ± 0.20[abc]	18.350	< 0.001

[a] Compared with that before treatment $p < 0.05$, [b] compared with that after treatment for 48 h $p < 0.05$, and [c] $p < 0.05$ *vs.* control group. Data are mean ± SD; FEV_1, Forced expiratory volume in one second; FVC, forced vital capacity; MVV, maximum voluntary ventilation.

Table 3 The patients' oxygen metabolism levels

Indicator	Time point for observation	Control group (n = 70)	Observation group (n = 70)	*t*	*P*-value
PaO_2 (mmHg)	Before treatment	43.54 ± 4.36	43.87 ± 4.52	0.440	0.661
	Following treatment for 48 h	59.84 ± 7.68[a]	65.54 ± 6.57[a]	4.719	< 0.001
	After treatment completion	77.95 ± 9.84[ab]	86.57 ± 11.01[abc]	4.884	< 0.001
CaO_2 (mL/L)	Before treatment	102.32 ± 13.42	103.10 ± 14.25	0.333	0.739
	Following treatment for 48 h	123.32 ± 10.87[a]	154.54 ± 12.98[a]	15.430	< 0.001
	After treatment completion	150.94 ± 14.53[ab]	166.75 ± 16.57[abc]	6.002	< 0.001
Oxygenation index (mmHg)	Before treatment	254.35 ± 20.93	255.36 ± 28.97	0.236	0.813
	Following treatment for 48 h	270.86 ± 23.41[a]	289.98 ± 30.42[a]	4.168	< 0.002
	After treatment completion	299.09 ± 24.56[ab]	311.23 ± 43.53[abc]	2.032	0.044

[a] By contrast with that before treatment $p < 0.05$, [b] compared to that after treatment for 48 h $p < 0.05$, and [c] $p < 0.05$ *vs*. control group. Data are mean ± SD. CaO_2, Arterial oxygen content; PaO_2, arterial oxygen partial pressure.

Table 4 The patients' airway hyper-reactivity parameters

Indicator	Time point for observation	Control group (n = 70)	Observation group (n = 70)	*t*	*P*-value
Inspiratory pressure (cmH_2O)	Before treatment	27.98 ± 3.42	28.12 ± 3.56	0.237	0.813
	Following treatment for 48 h	23.32 ± 2.13[a]	20.98 ± 2.32[a]	6.216	< 0.001
	After treatment completion	19.11 ± 1.23[ab]	17.87 ± 1.94[abc]	4.526	< 0.001
Peak airway pressure (cmH_2O)	Before treatment	34.53 ± 3.32	34.28 ± 2.35	0.514	0.608
	Following treatment for 48 h	32.17 ± 2.18[a]	30.18 ± 3.11[a]	4.383	< 0.001
	After treatment completion	26.45 ± 3.46[ab]	23.24 ± 2.86[abc]	5.983	< 0.001
Plateau pressure (cmH_2O)	Before treatment	17.75 ± 2.13	17.54 ± 2.34	0.555	0.580
	Following treatment for 48 h	14.53 ± 1.56[a]	11.28 ± 1.45[a]	12.770	< 0.001
	After treatment completion	11.54 ± 1.34[ab]	9.23 ± 1.00[abc]	11.560	< 0.001
Cdyn (mL/cmH_2O)	Before treatment	145.53 ± 16.57	144.48 ± 17.29	0.367	0.714
	Following treatment for 48 h	160.94 ± 17.56[a]	167.75 ± 19.09[a]	2.197	0.030
	After treatment completion	198.90 ± 10.64[ab]	203.42 ± 12.24[abc]	2.332	0.021

[a] In comparison to that before treatment $p < 0.05$, [b] by contrast to that after treatment for 48 h $p < 0.05$, and [c] $p < 0.05$ *vs*. control group. Data are mean ± SD. Cdy, Dynamic lung compliance.

Table 5 The airway remodeling indicators

Indicator	Time point for observation	Control group (n = 70)	Observation group (n = 70)	*t*	*P*-value
MMP-2	Before treatment	7.84 ± 1.02	7.80 ± 1.04	0.230	0.819
	Following treatment for 48 h	6.09 ± 0.78[a]	5.46 ± 0.76[a]	4.840	< 0.001
	After treatment completion	4.53 ± 0.57[ab]	3.42 ± 0.38[abc]	13.560	< 0.001
MMP-9	Before treatment	6.78 ± 1.23	6.70 ± 1.14	0.399	0.690
	Following treatment for 48 h	5.69 ± 0.97[a]	4.98 ± 0.70[a]	4.966	< 0.001
	After treatment completion	4.86 ± 0.65[ab]	3.42 ± 0.43[abc]	15.460	< 0.001
TIMP-2	Before treatment	2.70 ± 0.23	2.72 ± 0.21	0.537	0.592
	Following treatment for 48 h	2.30 ± 0.28[a]	1.80 ± 0.20a	12.160	< 0.001
	After treatment completion	1.89 ± 0.20[ab]	1.33 ± 0.19[abc]	16.980	< 0.001

[a] Compared with that before treatment $p < 0.05$, [b] compared with that after treatment for 48 h $p < 0.05$, and [c] $p < 0.05$ *vs*. control group. Data are mean ± SD ng/L. MMP, Matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase.

Inflammatory parameters. As explained by the data in Table 6, the levels of the inflammatory indicators IFN-γ, IL-4, IL-10, and IL-17 prior to treatment were comparable between the two groups but declined subsequent to the 48-h treatment and at treatment completion in both groups. Compared to the control group's values, those of the observation group were significantly lower ($p < 0.05$) (Table 6).

Clinical curative effects. Compared to the control group, the observation group displayed a significantly increased total response rate ($p < 0.05$) (Table 7).

28-day re-intubation rate. The observation group had a significantly lower 28-day re-intubation rate compared to the control group: 3 patients (4.29%) vs. 10 patients (14.29%), respectively ($p = 0.042$).

Discussion

AECOPD, a critical-status disease, is usually treated in clinical practice with invasive ventilation, and although invasive ventilation does provide a clear effect [10, 11], its long-term application may harm patients. For this reason, a PIC window is used as an indication for ventilation switching in COPD patients. The detection of a PIC window implies that a patient's symptoms have been preliminarily corrected, at which time the patient can be switched to noninvasive ventilation. If invasive ventilation is still applied after the detection of a PIC window, the risk of lung infection will increase, affecting the prognosis. In this study, we used the PIC window as the indication for ventilation switching in AECOPD patients, and we evaluated the clinical ability of HFNC with a PIC window as the indication for ventilation switching combined with atomizing inhalation of terbutaline to facilitate the recovery of such patients' lung function.

HFNC is a novel approach which has been confirmed to be markedly effective in treating COPD in clinical settings. It has been proposed that the benefits of HFNC are as follows [12-14]. (1) The oxygen concentration provided to patients by HFNC is significantly higher than that provided by oxygen inhalation, and this is helpful in improving patients' oxygenation function. (2) High-concentration oxygen can fill a

Table 6 The patients' inflammatory indicators

Indicator	Time point for observation	Control group (n = 70)	Observation group (n = 70)	*t*	*P*-value
IFN-γ	Before treatment	184.35 ± 20.32	183.98 ± 21.89	0.104	0.918
	Following treatment for 48 h	165.46 ± 18.98[a]	135.64 ± 15.46[a]	10.190	< 0.001
	After treatment completion	134.53 ± 17.58[ab]	123.42 ± 12.57[abc]	4.301	< 0.001
IL-4	Before treatment	75.64 ± 8.98	75.84 ± 9.12	0.131	0.896
	Following treatment for 48 h	56.75 ± 5.27[a]	50.93 ± 6.45[a]	5.846	< 0.001
	After treatment completion	40.29 ± 6.78[ab]	34.53 ± 3.27[abc]	6.402	< 0.001
IL-17	Before treatment	63.42 ± 9.98	63.56 ± 10.15	0.082	0.935
	Following treatment for 48 h	55.38 ± 7.57[a]	44.68 ± 5.47[a]	9.585	< 0.001
	After treatment completion	46.65 ± 6.65[ab]	40.93 ± 5.46[abc]	5.562	< 0.001
IL-10	Before treatment	5.34 ± 0.67	5.42 ± 0.84	0.623	0.534
	Following treatment for 48 h	3.57 ± 0.45[a]	2.08 ± 0.43[a]	20.030	< 0.001
	After treatment completion	1.99 ± 0.34[ab]	1.23 ± 0.25[abc]	15.070	< 0.001

[a] In comparison to that before treatment $p < 0.05$, [b] compared to that after treatment for 48 h $p < 0.05$, and [c] $p < 0.05$ *vs.* control group. Data are mean ± SD ng/mL. IFN-γ, Interferon gamma; IL, interleukin.

Table 7 The clinical efficacy of the treatment

Efficacy	Control group (n = 70)	Observation group (n = 70)	χ^2	*P*-value
Markedly effective	38 (54.29)	45 (64.29)		
Effective	20 (28.57)	11 (15.71)		
Ineffective	12 (17.14)	4 (5.71)		
Total response rate	58 (82.86)	66 (94.29)	4.516	0.034

Data are n (%).

patient's nasopharynx, reducing the physiological dead space, avoiding CO_2 inhalation, and repressing CO_2 retention. (3) The heated and humidified oxygen reduces the work of the breathing machine and increases the humidity of the nasal mucosa, which is beneficial for the excretion of sputum by airway cilia. (4) High oxygen flow forms positive airway pressure, thus decreasing atelectasis, enhancing a patient's pulmonary ventilation function, and changing abnormal oxygen metabolism. It has been reported that drug atomization therapy should also be provided for COPD patients during oxygen therapy [15]. Terbutaline, a drug that acts directly on bronchial smooth muscle, can suppress tissue edema induced by endogenous inflammatory mediators and the release of endogenous spasmodic substances, reducing airway resistance and enhancing a patient's pulmonary ventilation function. Our present findings revealed that HFNC with a PIC window as the indication for ventilation switching combined with atomizing inhalation of terbutaline significantly improved the lung function and lung compliance and markedly relieved pathological changes of airway hyper-reactivity in patients, achieving more satisfactory clinical efficacy.

These results may be attributed to the following two factors. (1) Heated and humidified oxygen is provided to patients by HFNC, filling the nasopharynx and washing the upper airway. As a result, the oxygen metabolism is changed, the pulmonary ventilation function is improved, and the lung compliance is increased, thereby facilitating the recovery of lung function [16]. (2) After the atomizing inhalation of terbutaline, the tissues with lesions are directly exposed to the drug, which can relax smooth muscle, relieve respiratory symptoms, and enhance the pulmonary ventilation function [17]. Moreover, the combination of HFNC with an atomizing inhalation of terbutaline exerts a synergistic effect that is capable of raising the gas exchange rate of the lungs.

Airway remodeling is a frequent pathological change in patients with COPD. The imbalance between MMPs and TIMPs leads to an increase in the serum levels of members of the MMP and TIMP families, impeding the degradation of the extracellular matrix. As a result, a massive amount of extracellular matrix is deposited on the bronchial wall, resulting in airway hyper-reactivity. In addition, MMP-2 and MMP-9 can recruit inflammatory cells to gather on the bronchial wall, aggravating the induced airway inflammation [18-20]. As an inhibitor of MMP-2, TIMP-2 has the ability to repress the activity of MMP-2. In COPD, an increase in the level of MMP-2 will lead to a compensatory increase of TIMP-2, giving rise to the deposition of elastin and collagen on the bronchial wall and thus resulting in airway remodeling [21].

Our present analyses revealed that the levels of MMP-2, MMP-9, and TIMP-2 were reduced in both patient groups after treatment, especially in the patients treated with HFNC combined with terbutaline. This result indicates that AECOPD patients have experienced airway remodeling that can be reversed by HFNC with a PIC window as the indication for ventilation switching combined with an atomizing inhalation of terbutaline, suggesting that this therapeutic regimen is effective for the treatment of AECOPD. We speculate that HFNC promotes the recruitment of collapsed lung areas through high-concentration oxygen in the presence of positive pressure, and that is augments the patient's pulmonary ventilation function and oxygenation level [22]. When this is combined with an atomizing inhalation of terbutaline, the proliferation and differentiation of epithelial cells as well as airway wall thickening are inhibited, thereby improving airway remodeling, which is manifested by reduced levels of MMP-2, MMP-9, and TIMP-2 [23].

The pathological mechanisms underlying COPD have been examined, and it was revealed that the immune imbalance mediated by T cells is a crucial player in the facilitation of disease development and progression. T helper 1 (Th1), Th2, and Th17 cells are important subsets of T cells, and among them, Th1 cells primarily secrete IFN-γ and other cytokines, which can improve the T-cell proliferation rate, strengthen the related effector cells in terms of their killing activity, and inhibit tissue remodeling [24,25]. Th2 cells secrete the proinflammatory factors IL-4 and IL-10. IL-4 stimulates B cells to secrete immunoglobulin E; it also induces eosinophils to secrete proinflammatory factors, and it participates in airway fibrosis [26,27]. IL-10 is able to repress the presentation of macrophage antigen and neutrophil aggregation, and a higher IL-10 level suggests a stronger anti-inflammatory effect and a stronger anti-inflammatory effect on airway inflammation [28]. Th17 cells mainly secrete IL-17, which causes airway obstruction by destroying lung parenchyma and increasing the secretion of airway mucus in COPD [29].

Under normal conditions, Th1, Th2 and Th17 cells are in dynamic balance, and their imbalance signifies that there are different degrees of immune-inflammatory lesions, which is considered an important pathological mechanism of persistent inflammation and airway remodeling in COPD [30, 31]. In the present study, decreased levels of IFN-γ and IL-4, -10, and -17 were observed after treatment, demonstrating the imbalance of Th17 and Th2 together with Th1 cells following AECOPD, which results in the elevation or compensatory increase of these cytokines.

The therapeutic regimen of HFNC with a PIC window as the indication for ventilation switching combined with an atomizing inhalation of terbutaline had a more definite inhibitory effect on inflammation, further suggesting that such a therapeutic regimen can facilitate the recovery of lung function — possibly by suppressing airway inflammation and correcting airway remodeling changes. We speculate that HFNC can induce temporary positive pressure in the respiratory tract and clear specific inflammatory cells in diseased tissues during inhalation. Terbutaline inhibits the inflammatory response by suppressing the infiltration of inflammatory substances induced by inflammatory mediators. Accordingly, the combination of the above-described HFNC regimen and terbutaline synergistically mitigates the airway or lung inflammatory response, providing beneficial conditions for symptom relief and disease recovery [32].

Our patients were followed up for 28 days, and compared with the patients treated with NIPPV with a PIC window as the indication for ventilation switching combined with the atomizing inhalation of terbutaline, the patients treated with HFNC with a PIC window as the indication for ventilation switching combined with the atomizing inhalation of terbutaline had a significantly lower 28-day re-intubation rate. This result may be ascribed to the fact that HFNC combined with terbutaline is more conducive to relieving pathological changes, eliminating the clinical symptoms and enhancing the lung function of patients.

Several study limitations should be considered. This was a single-center study with a small sample size, and the follow-up time was only 28 days. Our findings must be tested in studies with larger patient series and a longer follow-up period.

In conclusion, HFNC with a PIC window as the indication for ventilation switching combined with an atomizing inhalation of terbutaline can relieve the disorder of oxygen metabolism and correct airway hyper-reactivity, airway remodeling, and inflammation changes in patients with AECOPD, and it is more conducive to the recovery of these patients' lung function. This regimen also resulted in a low short-term prognostic re-intubation rate and a high response rate.

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