Reduction of PaCO$_2$ by high-flow nasal cannula in acute hypercapnic respiratory failure patients receiving conventional oxygen therapy

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Background: It has been suggested that a high-flow nasal cannula (HFNC) could help to remove carbon dioxide (CO$_2$) from anatomical dead spaces, but evidence to support that is lacking. The objective of this study was to elucidate whether use of an HFNC could reduce the arterial partial pressure of CO$_2$ (PaCO$_2$) in patients with acute hypercapnic respiratory failure who are receiving conventional oxygen (O$_2$) therapy.

Methods: A propensity score-matched observational study was conducted to evaluate patients treated with an HFNC for acute hypercapnic respiratory failure from 2015 to 2016. The hypercapnia group was defined as patients with a PaCO$_2$ > 50 mm Hg and arterial pH < 7.35.

Results: Eighteen patients in the hypercapnia group and 177 patients in the nonhypercapnia group were eligible for the present study. Eighteen patients in each group were matched by propensity score. Decreased PaCO$_2$ and consequent pH normalization over time occurred in the hypercapnia group (P = 0.002 and P = 0.005, respectively). The initial PaCO$_2$ level correlated linearly with PaCO$_2$ removal after the use of an HFNC ($R^2 = 0.378$, $P = 0.010$). The fraction of inspired O$_2$ used in the intensive care unit was consistently higher for 48 hours in the nonhypercapnia group. Physiological parameters such as respiratory rate and arterial partial pressure of O$_2$ improved over time in both groups.

Conclusions: Physiological parameters can improve after the use of an HFNC in patients with acute hypercapnic respiratory failure given low-flow O$_2$ therapy via a facial mask. Further studies are needed to identify which hypercapnic patients might benefit from an HFNC.

Key Words: hypercapnia; oxygen inhalation therapy; respiratory insufficiency

INTRODUCTION

The high-flow nasal cannula (HFNC) has several physiological benefits, one of which is to facilitate carbon dioxide (CO$_2$) washout from the airway system [1-3]. Although the theoretical background for CO$_2$ “sweeping” has been explained in various ways, previous studies have consistently reported improved ventilation after the use of an HFNC [4]. For example, breathing frequency and minute ventilation decrease without changing the arterial partial pressure of CO$_2$ (PaCO$_2$), which makes respiratory ventilation more efficient by decreasing the dead space [5,6]. Some researchers have suggested that reducing the overall dead space in the air-
way system can improve respiratory ventilation and ultimately help to remove CO_2_ [7,8]. Others have reported that the end-expiratory lung volume increases after the application of an HFNC, which might result in collapsed alveoli and increase gas flow [9,10]. However, the guidelines for managing acute hypercapnic respiratory failure recommend noninvasive ventilation (NIV) as the treatment of choice and suggest that an HFNC should not be used because of a lack of evidence for the benefits and the possibility of respiratory suppression [11,12]. Although intolerance or lung injury caused by the application of bilevel pressure has frequently been reported in patients treated with noninvasive or invasive ventilation, no alternative noninvasive options have been suggested [13,14].

Recent clinical trials have reported the benefits of using an HFNC to treat patients with obstructive lung disease or hypercapnia. The short-term application of an HFNC decreases the transcutaneous CO_2_ level and improves other physiological parameters in patients who require long-term oxygen (O_2_ therapy to treat stable chronic obstructive pulmonary disease (COPD)) [15]. For example, the PaCO_2_ level decreased more as the rate of gas flow in an HFNC increased in stable COPD patients [16]. In another study, HFNCs allowed patients with severe COPD to increase their exercise capacity without retaining CO_2_ [17]. Short-term use of an HFNC causes a decrease in transcutaneous CO_2_ levels even during an acute exacerbation of COPD [18]. Most of the previous studies on the use of an HFNC in treating hypercapnia have focused exclusively on relatively stable patients without considering patients with unstable hypercapnic status.

We conducted the present study to clarify whether, compared with nonhypercapnic patients, hypercapnic patients exhibit a tendency for CO_2_ retention or CO_2_ removal after the use of an HFNC. Our aim in the present study was to elucidate how physiological parameters change in relation to the initial PaCO_2_ level after the use of an HFNC in patients with acute respiratory failure given a facial mask for O_2_ therapy.

**MATERIALS AND METHODS**

**Study Population and Study Design**

This propensity score-matched cohort study was conducted by reviewing the electronic medical records in a tertiary teaching hospital. The study population comprised patients admitted to our hospital and given O_2_ therapy via an HFNC to manage acute respiratory failure between January 2015 and December 2016. The inclusion criteria were as follows: (1) the patient could breathe spontaneously without impaired men-

**KEY MESSAGES**

- After switching from conventional oxygen therapy with facial mask to high-flow nasal cannula, decrease in arterial partial pressure of carbon dioxide (PaCO_2_) consequent pH normalization, and recovery of respiratory rate were found during 48 hours among patients with acute hypercapnic respiratory failure.
- The amount of CO_2_ washout in the hypercapnia group was significantly related to the initial PaCO_2_ level but not to the respiratory rate or O_2_ flow rate.
- In propensity score-matched population, in-hospital mortality and mean survival time did not differ significantly between the hypercapnia and nonhypercapnia groups.

"After switching from conventional oxygen therapy with facial mask to high-flow nasal cannula, decrease in arterial partial pressure of carbon dioxide (PaCO_2_), consequent pH normalization, and recovery of respiratory rate were found during 48 hours among patients with acute hypercapnic respiratory failure. The amount of CO_2_ washout in the hypercapnia group was significantly related to the initial PaCO_2_ level but not to the respiratory rate or O_2_ flow rate. In propensity score-matched population, in-hospital mortality and mean survival time did not differ significantly between the hypercapnia and nonhypercapnia groups."
ulation of clinical outcomes, we reviewed in-hospital mortality, survived days, and cause of death.

**Assessment of Physiological and Clinical Outcomes**

The primary aim of this study was to determine the variation in PaCO\(_2\) level before and after HFNC application for 48 hours. The secondary aim was to assess the associations between the change in PaCO\(_2\) during the first 12 hours of HFNC use and the initial level of PaCO\(_2\), respiratory rate, and O\(_2\) flow rate in the hypercapnia group. We also analyzed the changes in other physiological parameters such as pH, PaO\(_2\), mean blood pressure, heart rate, and respiratory rate over time. The in-hospital mortality rate within 28 days, mean survival time within 28 days, and cause of mortality were evaluated.

**Table 1. Baseline characteristics in the total study population**

| Variable                          | Hypercapnia group (n=18) | Nonhypercapnia group (n=177) | P-value |
|-----------------------------------|--------------------------|-------------------------------|---------|
| Age (yr)                          | 70.5 ± 12.2              | 66.0 ± 13.1                   | 0.166   |
| Male sex                          | 16 (88.9)                | 116 (65.6)                    | 0.044   |
| Body mass index (kg/m\(^2\))      | 20.9 ± 2.7               | 21.4 ± 3.7                    | 0.601   |
| Glasgow coma scale                | 14.5 ± 1.2               | 14.9 ± 0.4                    | 0.243   |
| Do not resuscitate                | 11 (61.1)                | 95 (53.7)                     | 0.546   |
| Do not intubate                   | 7 (38.9)                 | 59 (33.3)                     | 0.635   |
| Department                        |                          |                               |         |
| Medical intensive care unit       | 18 (100)                 | 166 (93.8)                    | 0.276   |
| Previous history of ICU admission | 6 (33.3)                 |                               | -       |
| Underlying disease                |                          |                               |         |
| Cardiovascular disease            | 8 (44.4)                 | 34 (19.2)                     | 0.013   |
| Cardiomyopathy                    | 6 (33.3)                 | 46 (26.0)                     | 0.502   |
| Diabetes mellitus                 | 5 (27.8)                 | 49 (27.7)                     | 0.993   |
| Chronic respiratory disease       | 8 (44.4)                 | 46 (26.0)                     | 0.095   |
| Malignancy                        | 9 (50.0)                 | 107 (60.5)                    | 0.389   |
| Immune deficiency                 | 6 (33.3)                 | 109 (61.6)                    | 0.020   |
| Liver cirrhosis                   | 4 (22.2)                 | 17 (9.6)                      | 0.100   |
| Chronic kidney disease            | 5 (27.8)                 | 27 (15.3)                     | 0.172   |
| Blood test                        |                          |                               |         |
| Total white blood cell count (µl) | 16,000 ± 27,034          | 11,682 ± 8,323                | 0.509   |
| Hematocrit (%)                    | 32.5 ± 7.0               | 31.4 ± 5.8                    | 0.433   |
| Creatinine (mg/dl)                | 2.2 ± 2.1                | 1.4 ± 1.3                     | 0.161   |
| PH                                | 7.31 ± 0.09              | 7.43 ± 0.07                   | <0.001  |
| PaO\(_2\) (mm Hg)                 | 64.5 ± 21.4              | 73.0 ± 25.2                   | 0.168   |
| PaCO\(_2\) (mm Hg)                | 61.5 ± 15.1              | 34.6 ± 5.9                    | <0.001  |

Values are presented as mean ± standard deviation or number (%).

ICU: intensive care unit; PaO\(_2\): arterial partial pressure of oxygen; PaCO\(_2\): arterial partial pressure of carbon dioxide.

![Figure 1. Flowchart showing the classification and propensity score matching of acute respiratory failure patients. HFNC: high-flow nasal cannula.](https://www.accjournal.org)
Statistics

Categorical variables were compared using Pearson’s chi-square test or Fisher’s exact test. Continuous variables were analyzed using the Student t-test, and the results are described using the mean and standard deviation. We created propensity scores using logistic regression analyses with demographic characteristics, underlying disease, results of blood tests except for arterial blood gas analysis (ABGA), cause of respiratory failure, initial vital signs, use of inotropes, and severity in-

Table 2. Assessment of the clinical conditions in the total population

| Variable                                      | Hypercapnia group (n = 18) | Nonhypercapnia group (n = 177) | P-value |
|-----------------------------------------------|-----------------------------|--------------------------------|---------|
| Cause of respiratory failure^a               |                             |                                |         |
| Pneumonia                                     | 11 (61.1)                   | 121 (68.4)                     | 0.531   |
| Disease progression^b                        | 3 (16.7)                    | 21 (11.9)                      | 0.555   |
| Pulmonary edema                               | 6 (33.3)                    | 31 (17.5)                      | 0.103   |
| Acute exacerbation of COPD                    | 3 (16.7)                    | 10 (5.6)                       | 0.074   |
| Post-extubation respiratory failure          | 2 (11.1)                    | 16 (9.0)                       | 0.772   |
| Sepsis                                        | 1 (5.6)                     | 13 (7.3)                       | 0.779   |
| Pulmonary embolism                            | 0                           | 6 (3.4)                        | 0.428   |
| Other causes                                  | 1 (5.6)                     | 8 (4.5)                        | 0.842   |
| Initial vital sign                           |                             |                                |         |
| Mean blood pressure (mm Hg)                  | 91 ± 15                     | 92 ± 15.0                      | 0.537   |
| Heart rate (/min)                             | 101 ± 23                    | 103 ± 22                       | 0.736   |
| Respiratory rate (/min)                      | 29 ± 7                      | 27 ± 7                         | 0.434   |
| Body temperature (°C)                        | 37.4 ± 0.7                  | 37.4 ± 0.9                     | 0.931   |
| Oxygen saturation (%)                        | 90 ± 6                      | 90 ± 6                         | 0.609   |
| Use of inotropics                             |                             |                                |         |
| Dobutamine                                    | 0                           | 3 (1.7)                        | 0.567   |
| Dopamine                                      | 0                           | 11 (6.2)                       | 0.276   |
| Norepinephrine                                | 2 (11.1)                    | 14 (7.9)                       | 0.699   |
| Initial setting of high flow oxygen therapy  |                             |                                |         |
| O2 flow rate (L/min)                          | 43 ± 10                     | 42 ± 9                         | 0.555   |
| FiO2                                          | 0.58 ± 0.18                 | 0.66 ± 0.16                    | 0.037   |
| APACHE II score                               | 17.8 ± 7.1                  | 17.6 ± 6.3                     | 0.886   |
| SOFA score                                    | 6.2 ± 3.1                   | 6.5 ± 3.0                      | 0.662   |
| PF ratio                                      | 133 ± 92                    | 118 ± 54                       | 0.508   |

Values are presented as number (%) or mean ± standard deviation. COPD: chronic obstructive pulmonary disease; O2: oxygen; FiO2: fraction of inspired oxygen; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; PF ratio: PaO2/FiO2.

^aOne or more diseases were attributed to acute respiratory failure of each patient; ^bProgression of metastatic malignancy and chronic lung diseases such as interstitial lung disease and tuberculosis-destroyed lung are included.

Figure 2. Sequential measurements of arterial partial pressure of carbon dioxide (PaCO2, A), pH (B), and arterial partial pressure of oxygen (PaO2, C) during the use of a high-flow nasal cannula.
nonhypercapnia groups. Regression analysis with scatterplots was used to explain the relationships between CO₂ washout and other factors. We used R ver. 3.4.0 (R Core Team 2017, Vienna, Austria) for our statistical analyses.

Ethics
The Institutional Review Board of Seoul National University Hospital examined and approved the protocol for our study and exempted us from the need for informed consent to access to the electronic medical records (IRB No. H-1704-085-665).

RESULTS

Baseline Characteristics of the Study Population
In total, 195 patients were eligible and subsequently classified into two groups: 18 patients in the hypercapnia group and 177 in the nonhypercapnia group (Figure 1). All patients were supplied with 11–15 L of O₂ via a face mask before the application of an HFNC. In the analysis of the total study population, demographic features and the causes of respiratory failure showed significant heterogeneity between groups (Tables 1 and 2). Male sex and underlying cardiovascular disease were found more frequently in the hypercapnia group, and immune deficiency occurred in more patients in the nonhypercapnia group. The frequency of underlying chronic respiratory disease and acute exacerbation of COPD did not differ significantly between the two groups. A higher FiO₂ was applied to the nonhypercapnia group, but the O₂ flow rate was similar between groups. The initial vital signs, use of inotropes, and disease severity did not differ significantly between groups.

Eighteen patients in each group were matched one-to-one using the propensity score. The heterogeneity of the baseline characteristics and clinical features was adjusted and min-

### Table 3. Baseline characteristics in the propensity score-matched population

| Variable                              | Hypercapnia group (n = 18) | Nonhypercapnia group (n = 18) | P-value |
|---------------------------------------|----------------------------|--------------------------------|---------|
| Age (yr)                              | 70.5 ± 12.2                | 72.2 ± 9.3                    | 0.648   |
| Male sex                              | 16 (88.9)                  | 17 (94.4)                     | 0.546   |
| Body mass index (kg/m²)               | 20.9 ± 2.7                 | 20.8 ± 2.5                    | 0.879   |
| Glasgow coma scale                    | 14.5 ± 1.2                 | 14.8 ± 0.4                    | 0.378   |
| Do not resuscitate                    | 11 (61.1)                  | 10 (55.6)                     | 0.735   |
| Do not intubate                       | 7 (38.9)                   | 6 (33.3)                      | 0.729   |
| Department                            |                            |                               |         |
| Medical ICU                           | 18 (100)                   | 18 (100)                      | -       |
| Previous history of ICU admission     | 6 (33.3)                   | 6 (33.3)                      | 1.000   |
| Underlying disease                    |                            |                               |         |
| Cardiovascular disease                | 8 (44.4)                   | 11 (61.1)                     | 0.317   |
| Cardiomyopathy                        | 6 (33.3)                   | 8 (44.4)                      | 0.494   |
| Diabetes mellitus                     | 5 (27.8)                   | 5 (27.8)                      | 1.000   |
| Chronic respiratory disease           | 8 (44.4)                   | 11 (61.1)                     | 0.317   |
| Malignancy                            | 9 (50.0)                   | 6 (33.3)                      | 0.310   |
| Immune deficiency                     | 6 (33.3)                   | 4 (22.2)                      | 0.457   |
| Liver cirrhosis                       | 4 (22.2)                   | 3 (16.7)                      | 0.674   |
| Chronic kidney disease                | 5 (27.8)                   | 6 (33.3)                      | 0.717   |
| Blood test                            |                            |                               |         |
| Total white blood cell count (/μl)    | 16,000 ± 27,034            | 16,386 ± 11,984               | 0.956   |
| Hematocrit (%)                        | 32.5 ± 7.0                 | 33.3 ± 5.8                    | 0.721   |
| Creatinine (mg/dl)                    | 2.2 ± 2.1                  | 2.1 ± 1.5                     | 0.878   |
| pH                                    | 7.31 ± 0.09                | 7.42 ± 0.07                   | <0.001  |
| PaO₂ (mm Hg)                          | 64.5 ± 21.4                | 69.6 ± 28.1                   | 0.542   |
| PaCO₂ (mm Hg)                         | 61.5 ± 15.1                | 37.1 ± 6.1                    | <0.001  |

Values are presented as mean ± standard deviation or number (%).
ICU: intensive care unit; PaO₂: arterial partial pressure of oxygen; PaCO₂: arterial partial pressure of carbon dioxide.
One or more diseases were attributed to acute respiratory failure of each patient; progression of metastatic malignancy and chronic lung diseases such as interstitial lung disease and tuberculosis-destroyed lung are included.

Table 4. Assessment of clinical conditions in the propensity score–matched population

| Variable                      | Hypercapnia group (n=18) | Nonhypercapnia group (n=18) | P-value |
|-------------------------------|--------------------------|-----------------------------|---------|
| Cause of respiratory failurea |                          |                             |         |
| Pneumonia                     | 11 (61.1)                | 12 (66.7)                   | 0.729   |
| Disease progressionb          | 3 (16.7)                 | 2 (11.1)                    | 0.630   |
| Pulmonary edema               | 6 (33.3)                 | 7 (38.9)                    | 0.729   |
| Acute exacerbation of COPD    | 3 (16.7)                 | 5 (27.8)                    | 0.423   |
| Post-extubation respiratory failure | 2 (11.1)             | 2 (11.1)                    | 1.000   |
| Sepsis                        | 1 (5.6)                  | 1 (5.6)                     | 1.000   |
| Pulmonary embolism            | 0                       | 0                           | -       |
| Other causes                  | 1 (5.6)                  | 2 (11.1)                    | 0.546   |
| Initial vital sign            |                          |                             |         |
| Mean blood pressure (mm Hg)   | 91 ± 15                  | 91 ±13                      | 0.914   |
| Heart rate (/min)             | 101 ± 23                 | 99 ± 15                     | 0.786   |
| Respiratory rate (/min)       | 29 ± 7                   | 30 ± 6                      | 0.708   |
| Body temperature (°C)         | 37.4 ± 0.7               | 37.1 ± 0.7                  | 0.169   |
| Oxygen saturation (%)         | 90 ± 6                   | 90 ± 6                      | 0.775   |
| Use of inotropics             |                          |                             |         |
| Dobutamine                    | 0                       | 1 (5.6)                     | 1.000   |
| Dopamine                      | 0                       | 2 (11.1)                    | 0.486   |
| Norepinephrine               | 2 (11.1)                 | 1 (5.6)                     | 1.000   |
| Initial setting of high-flow O2 therapy |            |                             |         |
| O2 flow rate (L/min)          | 43 ± 10                  | 45 ± 8                      | 0.648   |
| FiO2                          | 0.58 ± 0.18              | 0.69 ± 0.16                 | 0.052   |
| APACHE II score              | 17.8 ± 7.1               | 17.7 ± 4.7                  | 0.956   |
| SOFA score                    | 6.2 ± 3.1                | 5.8 ± 2.3                   | 0.718   |
| PF ratio                      | 133 ± 92                 | 103 ± 39                    | 0.221   |

Values are presented as number (%) or mean ± standard deviation. COPD: chronic obstructive pulmonary disease; O2: oxygen; FiO2: fraction of inspired oxygen; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; PF ratio: PaO2/FiO2.

aOne or more diseases were attributed to acute respiratory failure of each patient.
bProgression of metastatic malignancy and chronic lung diseases such as interstitial lung disease and tuberculosis-destroyed lung are included.

mized, except for the targeted physiological parameters (Tables 3 and 4). The mean age was > 70 years, and about 90% of the patients were men. More than half of the patients had a declared “do not resuscitate order,” and about one-third of the patients had a declared “do not intubate order.” Pneumonia, pulmonary edema, and acute exacerbation of COPD were the main causes of respiratory failure. The initial mean respiratory rate was about 30 per minute, and the mean oxygen saturation was about 90%. The mean APACHE II score was about 18, and mean SOFA score was about 6. In the ABGA, the hypercapnia group had a lower pH (7.31 ± 0.09) and higher PaCO2 (61.5 ± 15.1 mm Hg). A higher FiO2 was used with the HFNC in the nonhypercapnia group.

Physiological Parameters in the Propensity Score–Matched Patients

The PaCO2 level changed over time, but the pattern of change differed between patient groups (P = 0.002 for the interaction of group and time) (Figure 2A). The PaCO2 level decreased over time (–11.2 ± 12.7 mm Hg for 48 hours) in the hypercapnia group but tended to increase over time (5.2 ± 12.2 mm Hg for 48 hours) in the nonhypercapnia group (P < 0.001 for the interaction of group and time).

In the hypercapnia group, the variation in PaCO2 during the first 12 hours was related to the initial PaCO2 level; that is, more CO2 was washed out by the HFNC in patients with a higher PaCO2 (R2 = 0.378, P = 0.010) (Figure 3). The decrease in PaCO2 was not related to the respiratory rate or O2 flow rate.

For pH, the pattern of change over time also differed between the groups (P = 0.005 for the interaction of group and time) (Figure 2B). The pH increased with time in the hypercapnia group but remained constant in the nonhypercapnia group. PaO2 increased over time in both groups (P = 0.001) (Figure 2C). All patients were supplied with 11–15 L of O2 via a facial mask before the application of an HFNC. The respiratory rate decreased similarly over time in both groups (P < 0.001) (Figure 4A). The heart rate had decreased at 12 hours and then increased slightly at 24 and 48 hours, but the changes with time...
Table 5. Clinical outcomes in the propensity score-matched population

| Variable                        | Hypercapnia group | Nonhypercapnia group | P-value |
|---------------------------------|-------------------|-----------------------|---------|
| All-cause mortality             | 10 (55.6)         | 11 (61.1)             | 0.735   |
| Cause of death                  |                   |                       | 0.867   |
| Respiratory failure             | 8 (80.0)          | 8 (72.7)              |         |
| Septic shock                    | 1 (10.0)          | 2 (18.2)              |         |
| Cardiac arrest                  | 1 (10.0)          | 1 (9.1)               |         |
| Others                          |                   |                       |         |
| Survival time during the 28 days after initiation of HFNC (day) | 16.9 ± 9.7 | 17.2 ± 5.4 | 0.522 |
| Day without HFNC in 7 days      | 1.9 ± 1.5         | 2.2 ± 1.8             | 0.687   |
| Day without HFNC in 14 days     | 8.8 ± 1.8         | 8.1 ± 3.7             | 0.462   |

Values are presented as number (%) or mean ± standard deviation.

HFNC: high-flow nasal cannula.

Figure 4. Sequential measurements of respiratory rate (A) and heart rate (B) during the use of a high-flow nasal cannula.

Figure 4. Sequential measurements of respiratory rate (A) and heart rate (B) during the use of a high-flow nasal cannula.

DISCUSSION

We found a significant decrease in PaCO₂ over time after use of an HFNC in patients with acute hypercapnic respiratory failure given O₂ therapy via a face mask. The amount of CO₂ washout in the hypercapnia group was significantly related to the initial PaCO₂ level but not to the respiratory rate or O₂ flow rate. Physiological parameters such as pH, PaO₂, and respiratory rate improved over time after the use of an HFNC in both groups. The applied O₂ flow rate did not differ significantly between the groups during the 48 hours of HFNC use. FiO₂ was consistently set higher in the nonhypercapnia group. In-hospital mortality and mean survival time did not differ significantly between the hypercapnia and nonhypercapnia groups.

Our results show that use of an HFNC in the hypercapnia group did not necessarily exacerbate CO₂ retention, but instead seemed to be beneficial for CO₂ removal, which was not observed in the nonhypercapnia group. This could indicate that the HFNC reduced the PaCO₂ level by increasing the clearance of CO₂ from anatomical dead spaces. Increased dead space is a well-known mechanism underlying hypercapnia and insufficient ventilation [20]. Rapid shallow breathing, which is commonly observed in acute respiratory failure, can increase...
the dead space, and increased dead space can contribute to hypercapnia [21]. Therefore, the patients in the hypercapnic group were more likely than those in the nonhypercapnic group to have had large dead-space ventilation. Our data thus suggest that the reduction in PaCO$_2$ in the hypercapnic group occurred through the HFNC “sweeping” CO$_2$ from the dead space.

Recent studies have shown that continuous positive airway pressure (CPAP) is beneficial for inducing CO$_2$ washout. In COPD and COPD overlap syndrome, CPAP can be useful for gas exchange in hypercapnic patients [22,23]. Our findings are consistent with those of a small prospective clinical study that showed that HFNC was more helpful for CO$_2$ reduction than a mask [24]. HFNC is primarily intended to provide a constantly high FiO$_2$, but it also supplies 1.5–3.1 cm H$_2$O of CPAP and reduces airway resistance [25,26]. The effects of HFNC on airway pressure or resistance could be one reason for the reduction in PaCO$_2$ in our study.

It is important to know why the patients in the hypercapnia group were not given NIV or invasive ventilation. Seven patients (or their family) refused to start NIV or invasive ventilation, and 11 patients could not tolerate NIV but could tolerate an HFNC. Even though four patients still exhibited CO$_2$ retention after use of an HFNC, NIV or mechanical ventilation was not applied because they refused that treatment. One patient was intubated after 48 hours. The decision to use an HFNC seemed to be heterogeneous and depended largely on each patient’s preference for or tolerance of the treatment modality.

CO$_2$ retention is caused by ventilatory impairment, which can result from various diseases [11]. Ventilation support with fractionated O$_2$ therapy is the principal therapy used to manage acute hypercapnia [25]. O$_2$ therapy with a high FiO$_2$ aggravates CO$_2$ retention in COPD patients [27]. However, an HFNC can supply a stable flow of O$_2$ with a high FiO$_2$. An HFNC is beneficial for oxygenation, but not ventilation, compared with conventional O$_2$ therapy [28]. Despite some controversy, several clinical trials involving an HFNC in hypercapnic patients have been conducted [15-18]. The background rationale for these trials is the physiological principle that efficient ventilation in the form of an HFNC could reduce dead space [7,8]. An HFNC could, therefore, be a promising alternative or intermediate option before the use of NIV because it has better clinical outcomes in some patients with acute respiratory failure [29]. Our study also shows how physiological parameters improved with time after the change from a face mask to an HFNC, which might have decreased the anatomic dead space. Although four patients in the hypercapnia group became worse with the use of an HFNC, there was sufficient time for them to try NIV again if requested. Given that the PaCO$_2$ changed little with use of an HFNC in patients from the hypercapnia group who died due to respiratory failure, a sufficient reduction in PaCO$_2$ with HFNC use might be a good prognostic indicator.

This study has several limitations. First, it was conducted retrospectively, and unknown confounding factors could not be controlled. However, we performed propensity score matching to minimize the effects of confounding variables. Second, our study population did not represent general patients with acute respiratory failure. Although pneumonia accounted for more than half of the causes of respiratory failure, our patients also had other causative diseases. A considerable number of patients had a terminal status and chose to use an HFNC to avoid invasive procedures or uncomfortable treatments. There-
fore, our study suggests that an HFNC might be tried before intubation in patients who cannot tolerate noninvasive positive ventilation, but it is unclear whether this would be beneficial in a specific causative disease. Third, patients who were intubated or noninvasively ventilated within 48 hours of HFNC use were excluded because their serial physiological parameters could have been affected by the use of supported gas ventilation. Fourth, we did not evaluate patients with a severe condition who needed immediate intubation for severe respiratory acidosis, a low level of consciousness, or intractable lung injury. Further studies are needed to identify which subgroups of patients with acute hypercapnic failure can benefit from the use of an HFNC. Finally, we could not confirm whether improvements in physiological parameters were related to better clinical outcomes. We analyzed a single arm from a cohort database in which the patients started HFNC when acute respiratory failure was diagnosed.

In conclusion, HFNC use decreased PaCO$_2$ in patients with various causes of acute hypercapnic respiratory failure. The results of the present study apply to the limited study population who used an HFNC for at least 48 hours.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: HWL, SML. Data curation & Formal analysis: HWL. Methodology: HWL, SMC, JL, YSP, SML. Project administration: HWL, SML. Visualization: HWL. Writing - original draft: HWL. Writing - review & editing: CHL, CGY, YWK, SKH, SML.

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