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Byung Ju Kang
Younsuck Koh
Chae-Man Lim
Jin Won Huh
Seunghee Baek
Myongja Han
Hyun-Suk Seo
Hee Jung Suh
Ga Jin Seo
Eun Young Kim
Sang-Bum Hong

Failure of high-flow nasal cannula therapy may delay intubation and increase mortality

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Take-home message: Using a high-flow nasal cannula for more than 48 h before intubation may increase the risk of adverse hospital outcomes for patients with respiratory failure. These patients exhibit lower extubation success, ventilator weaning, and ventilator-free days, and higher overall ICU mortality.

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B. J. Kang
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Ulsan College of Medicine, Ulsan University Hospital, Ulsan, South Korea

Y. Koh · C.-M. Lim · J. W. Huh · S.-B. Hong (✉)
Department of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea
e-mail: sbhong@amc.seoul.kr; hongsangbum@gmail.com
Tel.: 82-2-3010-3893

S. Baek
Department of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

M. Han · H.-S. Seo
Medical Emergency Team, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

H. J. Suh · G. J. Seo · E. Y. Kim
Intensive Care Nursing Team Respiratory Care Unit, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

Abstract *Purpose:* Intubation in patients with respiratory failure can be avoided by high-flow nasal cannula (HFNC) use. However, it is unclear whether waiting until HFNC fails, which would delay intubation, has adverse effects. The present retrospective observational study assessed overall ICU mortality and other hospital outcomes of patients who received HFNC therapy that failed. *Methods:* All consecutive patients in one tertiary hospital who received HFNC therapy that failed and who then required intubation between January 2013 and March 2014 were enrolled and classified according to whether intubation started early (within 48 h) or late (at least 48 h) after commencing HFNC. *Results:* Of the 175 enrolled patients, 130 (74.3 %) and 45 (25.7 %) were intubated before and after 48 h of HFNC, respectively. The groups were similar in terms of most baseline characteristics. The early intubated patients had better overall ICU mortality (39.2 vs. 66.7 %; $P = 0.001$) than late intubated patients. A similar pattern was seen with extubation success (37.7 vs. 15.6 %; $P = 0.006$), ventilator weaning (55.4 vs. 28.9 %; $P = 0.002$), and ventilator-free days (8.6 ± 10.1 vs. 3.6 ± 7.5; $P = 0.011$). In propensity-adjusted and -matched analysis, early intubation was also associated with better overall ICU mortality [adjusted odds ratio (OR) = 0.317, $P = 0.005$; matched OR = 0.369, $P = 0.046$]. *Conclusions:* Failure of HFNC might cause delayed intubation and worse clinical outcomes in patients with respiratory failure. Large prospective and randomized controlled studies on HFNC failure are needed to draw a definitive conclusion.

Keywords Oxygen inhalation therapy · Intubation · Noninvasive ventilation · Oxygen · Respiratory insufficiency

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Introduction

Oxygen supplementation is indispensable for maintaining the appropriate tissue oxygenation of patients with acute respiratory failure. Such patients require a high inspiratory flow that may vary from 30 to 120 l/min [1]. Conventional oxygen delivery methods include nasal cannula, simple mask, Venturi mask, and rebreathing mask. However, these devices can only provide a maximum oxygen flow of 6–15 l/min, which may be inadequate for patients with acute respiratory failure.

The high-flow nasal cannula (HFNC) is a novel oxygen supply device in a high-flow oxygen system that can deliver up to 100 % heated and humidified oxygen via a wide-bore nasal cannula at a maximum flow of 60 l/min [2]. It was recently reported to have beneficial effects on the clinical signs and oxygenation levels of patients with acute respiratory failure in intensive care units (ICUs) and emergency departments [3, 4]. Moreover, HFNC is superior to conventional oxygen therapies in terms of improving the dyspnea of extubated patients or patients with heart failure [5, 6].

In a recent randomized controlled study, HFNC provided to severe respiratory failure patients reduced the intubation rate and lowered ICU mortality [7]. Besides, HFNC might avoid the need for invasive mechanical ventilation [3, 8]. However, failure of HFNC may cause delayed intubation and increased mortality, like noninvasive ventilation (NIV) [9]. The primary objective of this study was ICU mortality according to the intubation timing in respiratory failure patients who received HFNC that failed. Secondary objectives were ventilator weaning, 14- and 28-day mortality, and length of ICU stay. We presented this study at the Congress of the Asian Pacific Society of Respirology [10].

Methods

Study design and subjects

We performed a retrospective observation study of critically ill patients older than 18 years who underwent intubation after HFNC failure and were treated in the ICU of Asan Medical Center, Korea, from January 2013 to March 2014. Considering the time to define early and late in NIV study [9], the cutoff value (46 h) analyzed by the receiver-operating characteristic curve, and practicality, patients with HFNC failure were divided into early and late groups based on whether intubation started before or after 48 h HFNC initiation. We compared the outcomes of both groups and adjusted our model using a propensity analysis. The study was approved by the Institutional Review Board of Asan Medical Center (IRB no. 2014-0803). Informed consent was not sought from patients because of the retrospective nature of the study.

HFNC device

In our hospital, patients with respiratory failure receive high-flow oxygen therapy via HFNC device (Optiflow^{TM}, Fisher & Paykel Healthcare, Auckland, New Zealand). This device is composed of an air-entrainment device (MaxVenturi^{TM}, Maxtec), heated humidification system (MR850 heated humidifier), heated humidification chamber (MR290 autofeed chamber), high-performance breathing circuit (RT202 single-limb adult breathing circuits kit), and a unique wide-bore nasal cannula (OPT 844 Optiflow^{TM} nasal cannula).

Monitoring of patients

All ICU patients usually receive continuous monitoring and multidisciplinary care involving three physicians (one resident, one intensivist, and one professor), nurses, pharmacists, respiratory therapists, and other divisions related to patient treatments. Patients in general wards are also managed by a medical emergency team with an electronic medical record-based screening system and a skilled intervention group (one intensivist, one senior resident, and two nurses) [11–13]. The medical emergency team has been carrying out proactive daily rounding of critically ill patients since 2008.

HFNC application and intubation

We routinely consult with an intensivist for HFNC application or intubation in patients with respiratory failure. HFNC is given to the following patients: those who exhibit hypoxia that requires a conventional oxygen device to deliver >9 l/min to achieve an oxygen saturation (SpO_2) of >92 %, those who show persistent signs of respiratory distress (respiration rate >24 breaths/min, accessory respiratory muscle use, and thoracoabdominal dyssynchrony) despite adequate oxygen supplementation [3], and those at risk of respiratory failure after extubation [14]. HFNC is not used in patients who require immediate intubation or have hypercapnia.

HFNC failure is defined as a need for endotracheal intubation despite HFNC application. We usually report the complete information to the patients and/or their families, communicating with them before intubation [15, 16]. After consent to the intubation, patients undergo rapid sequence intubation according to the protocol [17] and receive analgesics, sedative agents, and neuromuscular blocking agents based on the pain, agitation, and delirium guideline [8, 18]. The predetermined HFNC failure criteria are: hypoxemic respiratory failure with the patient expected to fail to maintain an SpO_2 <90 % despite receiving the maximal fraction of inspired oxygen (FiO_2) allowed by the HFNC; hypercapnic respiratory

failure accompanied by pH <7.3; respiration rate >35 breaths/min combined with respiratory distress; uncontrolled metabolic acidosis with hypotension (systolic blood pressure <90 mmHg or mean blood pressure <65 mmHg) despite fluid challenge and/or high-dose vasopressors; need for airway protection because of altered mental state or aspiration; cardiopulmonary arrest; or need for an operation to control the underlying disease [19].

Definitions

Successful extubation was defined as maintenance of spontaneous breathing for >48 h after interruption of mechanical ventilation with extubation. Ventilator weaning was defined as spontaneous breathing without a mechanical ventilator for >48 h in patients with tracheostomy or successful extubation. Use of immunosuppressive agents was defined as treatment with immunosuppressive drugs and/or a cumulative dose of >1,680 mg prednisolone equivalent within 6 months of HFNC [20]. Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were calculated by using the worst variable within the first 24 h of ICU admission.

Data collection

One respirologist reviewed all patient data (including baseline characteristics, severity indexes such as APACHE II and SOFA scores, etiology of respiratory failure, extubation and ventilator weaning, length of ICU stay, infectious and noninfectious complications, and cause of death) more than twice, and two professors in the respiratory division also rechecked the findings for accuracy.

The etiologies of respiratory failure before HFNC application were classified into six groups using a system modified from Demoule et al. [21]: acute de novo respiratory failure (i.e., pneumonia and acute respiratory distress syndrome), acute-on-chronic lung disease (i.e., chronic obstructive pulmonary disease and tuberculosis-destroyed lung), cardiogenic pulmonary edema, pulmonary edema due to renal failure, septic shock other than respiratory infection, and after extubation.

Statistical analysis

The data are expressed as median (interquartile range), mean ± standard deviation, or numbers (percentage). Categorical variables were compared using a chi-square test or McNemar test for matched patients. Continuous variables were compared using a Mann-Whitney U test or Wilcoxon signed-rank test for matched patients. $P < 0.05$ was considered to indicate statistical significance.

To reduce the effect of early and late HFNC therapy bias and potential confounding in this observational study, we conducted careful adjustment for differences in baseline characteristics (Table 1) using a propensity analysis [22]. Propensity scores were estimated by multiple logistic regression analysis (Table E1 in the Electronic Supplementary Material) by means of the stepwise backward elimination methods with $P < 0.20$.

The individual propensity score was integrated into each outcome model as a covariable. To compare hospital outcomes between early and late HFNC failure groups, we performed logistic regression (overall ICU mortality, extubation success, ventilator weaning, and 14- and 28-day mortality), negative binomial regression (length of ICU stay), and Cox proportional hazard regression (ventilator-free days) analysis. We also performed propensity score matching. To develop propensity score-matched pairs without replacement (a 1:1 match), the Greedy 5/1 digit match algorithm was used as reported previously [23, 24]. After all of the propensity score matches had been performed, we evaluated the balance in baseline covariables between the two groups. In the propensity score matched cohort, we conducted generalized estimating equations using logistic regression (overall ICU mortality, extubation success, ventilator weaning, and 14- and 28-day mortality) and negative binomial regression (length of ICU stay) to account for the clustering nature of matched pairs. Also, the Cox proportional hazard model (ventilator-free days) with the robust sandwich variance estimator was conducted. Analysis of results was performed using SPSS statistical software (version 21; SPSS, Chicago, IL, USA) and SAS software (version 9.3; SAS Institute, Cary, NC, USA).

Results

During the study period, 616 consecutive patients received HFNC at Asan Medical Center; 177 critically ill patients were intubated after HFNC failure after excluding 439 patients: those who improved and were weaned from HFNC ($n = 341$), those who deteriorated but were not intubated ($n = 85$), and those who used another oxygen device before intubation ($n = 13$). We further excluded two patients who were not transferred to the ICU. Of the remaining 175 patients, 130 underwent intubation before 48 h and 45 underwent intubation after 48 h of HFNC application (Fig. 1).

Table 1 Baseline characteristics and hospital outcomes for patients who were intubated after HFNC therapy failure

Characteristics	All patients ($n = 175$)	Early HFNC failure group ($n = 130$)	Late HFNC failure group ($n = 45$)	P value[a]
Age, years[b]	66 (57–74)	66 (56–73)	68 (57–75.5)	0.354
Male sex, *n* (%)	120 (68.6)	85 (65.4)	35 (77.8)	0.123
Body mass index, kg/m^2 [b]	21.8 (19.6–24.2)	22.2 (19.8–24.3)	21.1 (18.9–24.0)	0.326
HFNC treatment time, h[b]	17.8 (6.5–48.9)	10.1 (4.8–22.4)	126.1 (64.9–178.6)	<0.001
Underlying disease				
Diabetes mellitus, *n* (%)	51 (29.1)	44 (33.9)	7 (15.6)	0.020
Hypertension, *n* (%)	71 (40.6)	53 (40.8)	18 (40.0)	0.928
Solid malignancies, *n* (%)	43 (24.6)	34 (26.2)	9 (20.0)	0.409
Hematological malignancies, *n* (%)	55 (31.4)	40 (30.8)	15 (33.3)	0.749
Chronic kidney disease/dialysis, *n* (%)	22 (12.6)	18 (13.9)	4 (8.9)	0.387
Liver disease, *n* (%)	31 (17.7)	24 (18.5)	7 (15.6)	0.660
Use of immunosuppressive agents, *n* (%)	70 (40.0)	48 (36.9)	22 (48.9)	0.158
Coronary artery disease, *n* (%)	20 (11.4)	13 (10.0)	7 (15.6)	0.313
Heart failure, *n* (%)	30 (17.1)	22 (16.9)	8 (17.8)	0.896
Chronic obstructive pulmonary disease, *n* (%)	21 (12.0)	15 (11.5)	6 (13.3)	0.749
Tuberculosis-destroyed lung, *n* (%)	31 (17.7)	19 (14.6)	12 (26.7)	0.068
PaO_2/FiO_2 before HFNC, mmHg[b]	165.6 (118.0–235.7) ($n = 172$)	158.6 (112.7–222.8) ($n = 129$)	180.0 (138.4–292.0) ($n = 43$)	0.061
PaO_2/FiO_2 before intubation, mmHg[b]	88.0 (67.0–148.6)	90.6 (69.7–149.0)	86.3 (64.3–156.7)	0.594
APACHE II score[b]	25.0 (21.0–28.0)	25.0 (21.0–28.0)	25.0 (21.0–28.5)	0.832
SOFA score[b]	9.0 (6.0–12.0)	10.0 (7.0–13.0)	7.0 (5.0–11.0)	0.007
Etiology of respiratory failure before HFNC application				
Acute de novo respiratory failure, *n* (%)	58 (33.1)	43 (33.1)	15 (33.3)	0.975
Acute-on-chronic lung disease, *n* (%)	53 (30.3)	37 (28.5)	16 (35.6)	0.372
Cariogenic pulmonary edema, *n* (%)	14 (8.0)	11 (8.5)	3 (6.7)	>0.999
Pulmonary edema due to renal failure, *n* (%)	6 (3.4)	5 (3.8)	1 (2.2)	>0.999
Septic shock other than respiratory infection, *n* (%)	15 (8.6)	12 (9.2)	3 (6.7)	0.763
After extubation, *n* (%)	29 (16.6)	22 (16.9)	7 (15.6)	0.832
Primary outcome				
Overall ICU mortality, *n* (%)	81 (46.3)	51 (39.2)	30 (66.7)	0.001
Secondary outcomes				
Extubation success, *n* (%)	56 (32.0)	49 (37.7)	7 (15.6)	0.006
Ventilator-weaning, *n* (%)[c]	85 (48.6)	72 (55.4)	13 (28.9)	0.002
Ventilator-free days to day 28[b]	7.3 ± 9.7	8.6 ± 10.1	3.6 ± 7.5	0.001
14-Day mortality from HFNC application, *n* (%)	53 (30.3)	39 (30.0)	14 (31.1)	0.889
14-Day mortality from intubation, *n* (%)	61 (34.9)	42 (32.3)	19 (42.2)	0.229
28-Day mortality from HFNC application, *n* (%)	83 (47.4)	60 (46.2)	23 (51.1)	0.566
28-Day mortality from intubation, *n* (%)	87 (49.7)	60 (46.2)	27 (60.0)	0.109
Length of ICU stay[b]	12.0 (5.0–22.0)	11.0 (5.0–19.3)	16.0 (7.5–28.5)	0.065

HFNC high-flow nasal cannula, *PaO_2/FiO_2* ratio of partial pressure arterial oxygen and fraction of inspired oxygen, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment

[a] Statistical comparisons of the data were performed using the chi-square test for categorical variables and Mann-Whitney *U* test for continuous variables

[b] Continuous variables are presented as median (interquartile range) or mean ± standard deviation

[c] Includes both extubation and tracheostomy weaning

Patient characteristics

The characteristics of all 175 patients and both groups are shown in Table 1. Many patients had underlying diseases such as immunosuppressive agents use [40.0 % (70/175)], hematological malignancies [31.4 % (55/175)], and solid malignancies [24.6 % (43/175)]. The SOFA score was higher in the early HFNC failure group than in the late HFNC failure group.

Etiology of respiratory failure

The main etiologies of respiratory failure indicating HFNC application are presented in Table 1. The most common etiologies for respiratory failure were acute de novo respiratory failure [33.1 % (43/130)] and acute-on-chronic lung disease [35.6 % (16/45)] in the early and late HFNC failure groups, respectively. However, there was no significant difference between the two groups.

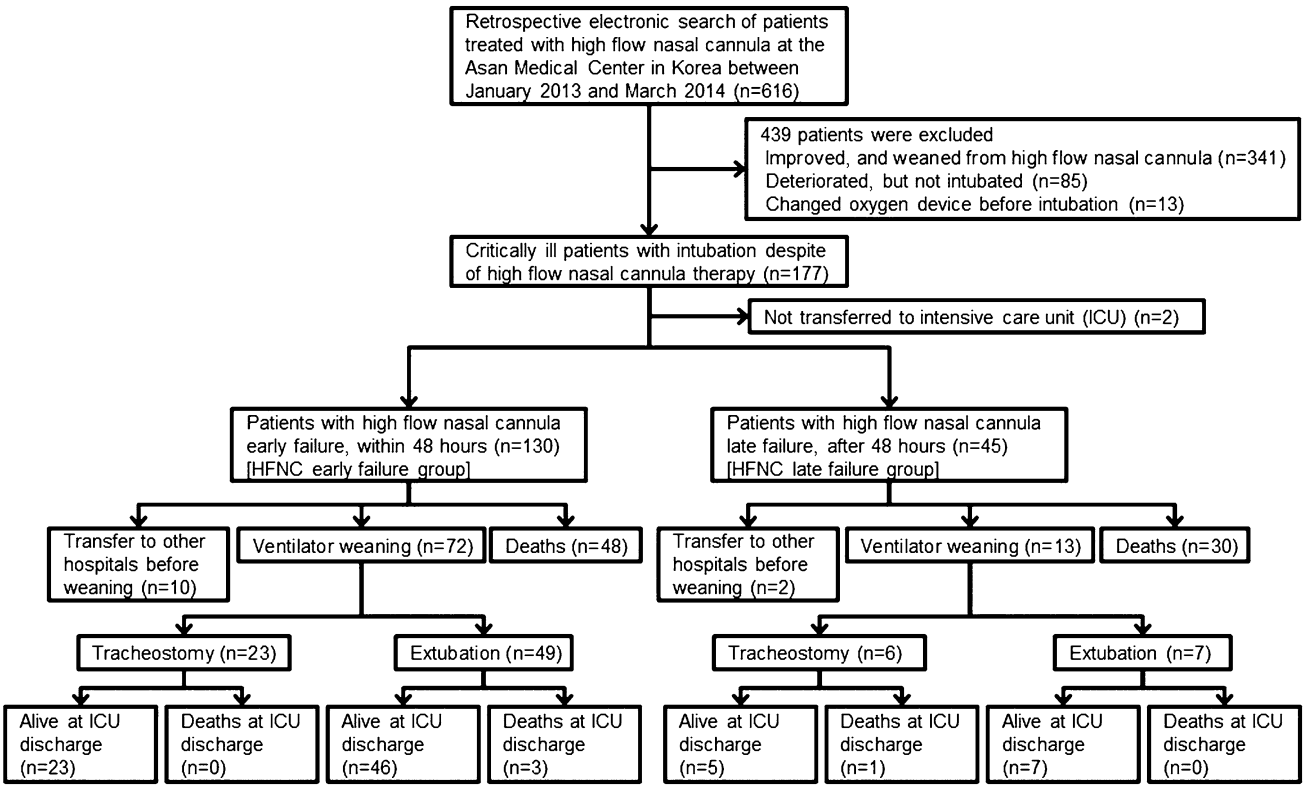

Fig. 1 Distribution of the study population according to HFNC therapy outcome

The causes of HFNC application and intubation are shown in Table E2 in the Electronic Supplementary Material.

ICU outcomes

The early and late groups did not differ significantly in terms of 14-day mortality, 28-day mortality, or length of ICU stay. However, the early group had better ICU outcomes than the late group (Table 1): they were significantly more likely to have better overall ICU mortality (39.2 vs. 66.7 %; $P = 0.001$), extubation success (37.7 vs. 15.6 %; $P = 0.006$), ventilator weaning (55.4 vs. 28.9 %; $P = 0.002$), and ventilator-free days to day 28 (8.6 ± 10.1 vs. 3.6 ± 7.5; $P = 0.001$).

Propensity score adjusted and matched ICU outcomes

We confirmed the discrimination and calibration of the model by assessing the *c*-statistics ($c = 0.766$) and Hosmer-Lemeshow statistics ($P = 0.353$), respectively. After propensity score matching, we selected 37 pairs of patients with similar baseline characteristics, severity indexes (PaO_2/FiO_2, APACHE II score, and SOFA score), and etiology of respiratory failure (Table 2). Propensity score-adjusted and -matched analysis showed that intubation before 48 h of HFNC was associated with better overall ICU mortality [adjusted odds ratio (OR) = 0.317, $P = 0.005$; matched OR = 0.369, $P = 0.046$], extubation success (adjusted OR = 3.091, $P = 0.020$), ventilator weaning (adjusted OR = 3.380, $P = 0.004$; matched OR = 2.495, $P = 0.041$), and ventilator-free days [adjusted hazard ratio (HR) = 0.516, $P = 0.001$; matched HR = 0.639, $P = 0.026$] (Table 3).

Complications on ICU admission and during ICU stay and events leading to death

As shown in Table 4, the most frequent presenting complication on ICU admission in both groups was pneumonia (66.9 vs. 80.0 %), and it was the leading cause of death in the ICU [29.6 % (24/81) vs. 21.6 % (11/51)]. During ICU stay, renal failure was the most frequent complication in both groups (25.4 vs. 37.8 %). Most complications during ICU stay were more frequent in the late HFNC failure group than in the early HFNC failure group, but there were no significant differences between the two groups except for cardiac dysfunction (10.8 vs. 31.1 %; $P = 0.001$).

Table 2 Baseline characteristics of the early and late HFNC failure group after matching on propensity score

	Early HFNC failure group ($n = 37$)	Late HFNC failure group ($n = 37$)	P value[a]
Age, years[b]	69.0 (58.0–75.0)	68.0 (57.0–75.5)	0.814
Male sex, *n* (%)	28 (75.7)	27 (73.0)	>0.999
Body mass index (kg/m^2)[b]	22.1 (19.4–23.4)	21.3 (19.2–24.2)	0.678
Underlying disease			
Diabetes mellitus, *n* (%)	6 (16.2)	6 (16.2)	>0.999
Hypertension, *n* (%)	14 (37.8)	14 (37.8)	>0.999
Solid malignancies, *n* (%)	10 (27.0)	9 (24.3)	>0.999
Hematological malignancies, *n* (%)	11 (29.7)	12 (32.4)	>0.999
Chronic kidney disease/dialysis, *n* (%)	3 (8.1)	4 (10.8)	>0.999
Liver disease, *n* (%)	5 (13.5)	6 (16.2)	>0.999
Use of immunosuppressive agents, *n* (%)	9 (24.3)	15 (40.5)	0.238
Coronary artery disease, *n* (%)	7 (18.9)	7 (18.9)	>0.999
Heart failure, *n* (%)	7 (18.9)	6 (16.2)	>0.999
Chronic obstructive pulmonary disease, *n* (%)	4 (10.8)	3 (8.1)	>0.999
Tuberculosis-destroyed lung, *n* (%)	10 (27.0)	8 (21.6)	0.774
PaO_2/FiO_2 before HFNC, mmHg[b]	167.7 (122.9–219.3)	176.6 (137.6–254.6)	0.660
PaO_2/FiO_2 before intubation, mmHg[b]	99.6 (74.0–140.2)	84.0 (59.3–121.7)	0.531
APACHE II score[b]	23.0 (21.0–28.5)	24.0 (21.0–29.0)	0.869
SOFA score[b]	7.0 (5.5–11.0)	9.0 (5.0–11.0)	0.862
Etiology of respiratory failure before HFNC application			
Acute de novo respiratory failure, *n* (%)	9 (24.3)	13 (35.1)	0.481
Acute-on-chronic lung disease, *n* (%)	12 (32.4)	10 (27.0)	0.804
Cariogenic pulmonary edema, *n* (%)	4 (10.8)	3 (8.1)	>0.999
Pulmonary edema due to renal failure, *n* (%)	1 (2.7)	1 (2.7)	>0.999
Septic shock other than respiratory infection, *n* (%)	4 (10.8)	3 (8.1)	0.344
After extubation, *n* (%)	7 (18.9)	7 (18.9)	>0.999

HFNC high-flow nasal cannula, *PaO_2/FiO_2* ratio of partial pressure arterial oxygen and fraction of inspired oxygen, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment

[a] Statistical comparisons of the data were performed using the McNemar test for categorical variables and the Wilcoxon signed-rank test for continuous variables

[b] Continuous variables are presented as median (interquartile range)

Discussion

Our current study findings suggest that early intubation (i.e., within 48 h of starting HFNC) is associated with lower overall ICU mortality than late intubation (i.e., after 48 h of starting HFNC) when patients had received HFNC therapy that failed. In addition, early intubation was found to be associated with better extubation success and ventilator weaning and more ventilator-free days than late intubation. Although several previous studies have assessed the failure of NIV in patients with respiratory failure [9, 25], our present study is, to our knowledge, the first to assess HFNC failure. Moreover, our present study sought to identify the proper HFNC management strategy by analyzing patients with HFNC failure.

HFNC has many advantages as a treatment of acute respiratory failure. First, the heated humidifier system of HFNC improves mucociliary function and secretion expectoration [2] and decreases the metabolic cost of gas conditioning [26]. Second, the high flow achieved by HFNC can improve patient oxygenation [26], generate low-level positive airway pressure [27], reduce the respiration rate of patients [28], attenuate inspiratory resistance [26], and supply a constant FiO_2 [29]. Third, HFNC allows the patient to speak and cough and permits oral intake [4]. It is also better tolerated and more comfortable than a face mask [2, 30]. Fourth, HFNC therapy does not increase the risk of complications such as pneumonia, barotraumas, or secondary infections [31].

Despite the advantages of HFNC in patients with respiratory failure, its inappropriate use can be hazardous to patient health. One study has stated that patients who are not intubated tolerate HFNC for long periods and that HFNC is safe for managing patients with respiratory failure for several days [32]. However, our present study findings contradict those conclusions. Thus, extended use of HFNC before intubation in patients with respiratory failure may be harmful.

An earlier study on NIV therapy reported that, of patients who were admitted to the ICU for acute respiratory

Table 3 Analysis of hospital outcomes for the early HFNC failure group compared with the late HFNC failure group (as reference) using the propensity score analysis

Variables	Crude		Propensity-adjusted[a]		Propensity-matched[b]	
	Odds ratio (95 % CI)	*P* value[c]	Odds ratio (95 % CI)	*P* value[c]	Odds ratio (95 % CI)	*P* value[c]
Primary outcome						
Overall ICU mortality	0.323 (0.158–0.658)	0.002	0.317 (0.143–0.700)	0.005	0.369 (0.139–0.984)	0.046
Secondary outcomes						
Extubation success	3.284 (1.361–7.923)	0.008	3.091 (1.193–8.013)	0.020	2.057 (0.746–5.672)	0.163
Ventilator-weaning	3.056 (1.470–6.351)	0.003	3.380 (1.492–7.656)	0.004	2.495 (1.039–5.991)	0.041
Ventilator-free days to day 28	0.542 (0.383–0.768)[d]	0.001[e]	0.516 (0.349–0.763)[d]	0.001[e]	0.639 (0.431–0.946)[d]	0.026[e]
14-Day mortality from HFNC application	0.949 (0.455–1.977)	0.888	0.712 (0.312–1.622)	0.418	0.608 (0.231–1.606)	0.316
14-Day mortality from intubation	0.653 (0.325–1.311)	0.231	0.482 (0.218–1.067)	0.072	0.447 (0.168–1.184)	0.105
28-Day mortality from HFNC application	0.820 (0.416–1.616)	0.566	0.680 (0.318–1.457)	0.322	0.896 (0.440–1.824)	0.763
28-Day mortality from intubation	0.571 (0.287–1.138)	0.111	0.557 (0.258–1.198)	0.134	0.802 (0.380–1.692)	0.563
Length of ICU stay	0.827 (0.586–1.169)[f]	0.282[g]	0.830 (0.552–0.800)[f]	0.372[g]	1.329 (0.598–2.952)[f]	0.485[g]

HFNC high-flow nasal cannula, *CI* confidence interval, *ICU* intensive care unit

[a] The individual propensity score was integrated into each outcome model as a covariable (all study patients were included)

[b] Of the 175 patients, 37 pairs were matched

[c] Statistical comparisons of the data were performed using logistic regression analysis

[d] Hazard ratios analyzed by Cox proportional hazard regression model

[e] Statistical comparisons of the data were performed using Cox proportional hazard regression analysis

[f] Relative ratio by negative binomial regression model

[g] Statistical comparisons of the data were performed using negative binomial regression analysis

failure, those who immediately underwent invasive mechanical ventilation had lower in-hospital mortality than those who only underwent invasive mechanical ventilation after NIV failure [33]. A review of Ozyilmaz et al. [25] reported that NIV failure was strongly associated with poor outcomes and that prompt endotracheal intubation should be performed if early or late signs of deterioration are detected. Moreover, Moretti et al. found that late NIV failure (>48 h after starting NIV) was associated with particularly high mortality (67.7 %) and poor prognosis [9]. Similarly, in our present study, the time to define early and late was 48 h, and late HFNC failure was associated with higher overall ICU mortality compared with early HFNC failure. This result may be because prolonged intubation delay in patients with uncontrolled disease can induce respiratory muscle fatigue and cardiac dysfunction, which in turn lead to poor hospital outcomes.

Our data showed that there were no statistical differences in 14- and 28-day mortality, but overall ICU mortality was higher in the late HFNC failure group than early HFNC failure group. This was probably because more patients in the early HFNC failure group died following ICU discharge and more patients in the late HFNC failure group died in the ICU after prolonged ventilation of more than 28 days. Although we analyzed hospital outcomes according to HFNC failure, we could not determine how to anticipate the patients with late HFNC failure. There were no statistical differences in most baseline characteristics between the early and late HFNC failure groups. Diabetes mellitus and the SOFA score were somewhat higher in the early HFNC failure group. Future prospective randomized studies are certainly warranted to address this question.

Limitations

This study had several limitations. First, it was a retrospective observational study. However, we used propensity score matching and evaluated the influence of HFNC failure in a group of carefully selected patients to identify a possible link between late HFNC failure and poor hospital outcomes. Our retrospective data on early and late HFNC failure may represent a major departure from the data that would be available for such a comparison from a randomized controlled study. Second, the study was conducted in a single tertiary referral center, although we recruited many patients. Selection bias cannot be excluded, and the results should be carefully interpreted. Larger scale multicenter studies are required to confirm the results. Third, the actual delivered FiO_2 was not measured; we cannot definitively state that the FiO_2 with HFNC was truly higher than the FiO_2 with conventional oxygen devices. The PaO_2/FiO_2 data should be interpreted with caution. Nevertheless, we believe that HFNC does deliver more FiO_2 than conventional devices because the oxygenation and respiratory variables of our patients improved when HFNC was applied. Fourth, our

Table 4 Serious complications presented on ICU admission and occurring during ICU stay and events leading to death in patients with HFNC failure

Total number of complications/ number of causing death in ICU	Presented on ICU admission			Occurred during ICU stay		
	Early HFNC failure group ($n = 130$)	Late HFNC failure group ($n = 45$)	P value[a]	Early HFNC failure group ($n = 130$)	Late HFNC failure group ($n = 45$)	P value[a]
Infectious complications						
Pneumonia, *n* (%)	87/24 (66.9)	36/11 (80.0)	0.130	12/2 (9.2)	7/3 (15.6)	0.269
VAP, *n* (%)	–	–	–	18/5 (13.8)	10/4 (22.2)	0.187
CRBSI, *n* (%)	2/0 (1.5)	–	>0.999	9/0 (6.9)	5/0 (11.1)	0.356
Hepatobiliary or gastrointestinal infection, *n* (%)	12/2 (9.2)	4/3 (8.9)	>0.999	7/1 (5.4)	2/1 (4.4)	>0.999
Other infectious causes, *n* (%)[b]	5/2 (3.8)	2/0 (4.4)	>0.999	2/0 (1.5)	1/0 (2.2)	>0.999
Noninfectious complications						
Cardiac dysfunction, *n* (%)[c]	18/2 (13.8)	5/1 (11.1)	0.640	14/2 (10.8)	14/2 (31.1)	0.001
Renal failure, *n* (%)	12/0 (9.2)	2/0 (4.4)	0.524	33/0 (25.4)	17/0 (37.8)	0.113
Hepatic failure, *n* (%)	9/5 (6.9)	–	0.114	2/0 (1.5)	1/0 (2.2)	>0.999
Pulmonary toxicity related treatments, *n* (%)[d]	4/0 (3.1)	4/1 (8.9)	0.206	–	–	–
Myocardial infarction, *n* (%)	4/1 (3.1)	–	0.574	1/0 (0.8)	2/0 (4.4)	0.163
Cerebral infarction, *n* (%)	2/1 (1.5)	1/0 (2.2)	>0.999	2/0 (1.5)	–	>0.999
Pulmonary thromboembolism, *n* (%)	2/0 (1.5)	–	>0.999	2/0 (1.5)	–	>0.999
Pneumothorax, *n* (%)	2/0 (1.5)	1/0 (2.2)	>0.999	9/0 (6.9)	–	0.114
Gastrointestinal bleeding, *n* (%)	6/1 (4.6)	1/0 (2.2)	0.679	5/1 (3.8)	5/1 (11.1)	0.127
Extra-gastrointestinal bleeding, *n* (%)	5/0 (3.8)	1/0 (2.2)	>0.999	6/1 (4.6)	4/2 (8.9)	0.283
DIC, *n* (%)[e]	3/0 (2.3)	1/0 (2.2)	>0.999	9/0 (6.9)	5/0 (11.1)	0.356
Cardiopulmonary resuscitation, *n* (%)	2/0 (1.5)	1/0 (2.2)	>0.999	6/1 (4.6)	4/1 (8.9)	0.283
Other noninfectious causes, *n* (%)[f]	3/0 (2.3)	1/0 (2.2)	>0.999	–	–	–

ICU intensive care unit, *HFNC* high-flow nasal cannula, *VAP* ventilator associated pneumonia, *CRBSI* catheter-related bloodstream infection, *DIC* disseminated intravascular coagulation

[a] Statistical comparisons of the data were performed using a Mann-Whitney *U* test

[b] Other infectious causes of ICU admission consisted of surgical site infection (1), mediastinitis (1), and unknown origin sepsis (3) in the early HFNC failure group and diabetic foot infection (1) and unknown origin sepsis (1) in the late HFNC failure group. Other infectious causes during ICU admission consisted of urinary tract infection (1) and unknown origin sepsis (1) in the early HFNC failure group and kidney cyst infection (1) in the late HFNC failure group

[c] Echocardiographic or portable ICU ultrasound confirmed

[d] Pulmonary toxicity-related treatments of ICU admission consisted of gefitinib-induced pulmonary toxicity (1), paclitaxel-induced pulmonary toxicity (1), etoposide-induced pulmonary toxicity (1) and transfusion-related acute lung injury (1) in the early HFNC failure group and rituximab-induced pulmonary toxicity (1), docetaxel-induced pulmonary toxicity (1), radiation-induced pulmonary toxicity (1) and transfusion-related acute lung injury (1) in the late HFNC failure group

[e] We set a DIC score (proposed by the International Society of Thrombosis and Haemostasis) of 5 or higher as being compatible with DIC

[f] Other noninfectious causes of ICU admission consisted of a hyperosmolar hyperglycemic state (1), postoperation (1), and re-expansion pulmonary edema (1) in the early HFNC failure group and postoperation (1) in the late HFNC failure group

study focused on patients with HFNC failure, not patients who had been weaned off HFNC. Therefore, there is a possibility, albeit low, that we might have missed patients with re-respiratory failure after HFNC weaning. Fifth, the patients included in our study exhibited high overall ICU mortality, reflecting the high frequency of poor prognosis factors such as immunosuppressive agent use [34], hematological malignancy [35], and solid malignancy [36]. The patients also frequently had low PaO_2/FiO_2 ratios and high APACHE II scores compared with patients in previous studies [9, 14, 37]. The study protocol, which stipulated that only patients with treatment failure should be enrolled, is likely to have contributed to the high mortality rate. Finally, we are unable to exclude the possibility of not keeping the predetermined criteria of HFNC failure and need for intubation because of the retrospective study. However, this was less likely because all our patients received management by a skilled medical emergency team, and they underwent continuous monitoring or screening [13].

Conclusions

HFNC is a novel and attractive oxygen device for patients with respiratory failure. However, its inappropriate use may lead to adverse outcomes. In our study, failure of HFNC late (>48 h) after its initiation was associated with significantly higher overall ICU mortality, poorer extubation success and ventilator weaning, and fewer ventilator-free days. Our findings suggest that larger

prospective randomized trials on HFNC failure in respiratory failure patients are warranted.

Conflicts of interest The authors have no conflicts of interest to declare.

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