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Efficacy of High-Flow Nasal Cannula Therapy in Acute Hypoxemic Respiratory Failure: Decreased Use of Mechanical Ventilation

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BACKGROUND: We evaluated the efficacy of high-flow nasal cannula (HFNC) therapy, a promising respiratory support method for acute hypoxemic respiratory failure (AHRF). METHODS: We conducted a retrospective single-center cohort study comparing the periods before (June 2010 to May 2012) and after (June 2012 to May 2014) HFNC introduction (pre- and post-HFNC periods). During these periods, we retrieved cases of AHRF treated with any respiratory support (invasive ventilation, noninvasive ventilation [NIV], and HFNC) and compared in-hospital mortality, ICU/intermediate care unit/hospital stay, and need for mechanical ventilation. RESULTS: Eighty-three subjects (65 treated with NIV, and 18 treated with invasive ventilation) and 89 subjects (33 treated with HFNC, 43 treated with NIV, and 13 treated with invasive ventilation) identified from 782 pre-HFNC and 930 post-HFNC records of acute respiratory failure who required emergent admissions to the respiratory care department were analyzed. Overall, the in-hospital mortality rate was similar, although there was a non-significant and slight decrease from 35 to 27% ($P = .26$). There was no significant difference among ICU, intermediate care unit ($P = .80$), and hospital ($P = .33$) stay. In the post-HFNC period, significantly fewer subjects required mechanical ventilation (NIV or invasive ventilation) (100% vs 63%, $P < .01$). Additionally, there were significantly fewer ventilator days (median [interquartile range] of 5 [2–11] vs 2 [1–5] d, $P < .05$) and more ventilator-free days (median [interquartile range] of 18 [0–25] vs 26 [20–27] d, $P < .01$). CONCLUSIONS: HFNC might be an alternative for AHRF subjects with NIV intolerance. *Key words: acute hypoxemic respiratory failure; respiratory support; high-flow nasal cannula; invasive ventilation; noninvasive ventilation; ventilator-free days.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Acute respiratory failure (ARF) is a fatal complication of various respiratory diseases. It is the cause of ~30% of ICU admissions and is associated with adverse outcomes.[1,2] Despite early and appropriate treatment, ARF may persist. Optimum oxygen administration is critical to maintain satisfactory oxygenation during this critical period.

Noninvasive ventilation (NIV) has been increasingly used to manage ARF of various etiologies.[3,4] NIV is associated not only with less need for endotracheal intubation, but also with reduced occurrence of complications (eg, nosocomial infections), decreased ICU stay, and lower overall cost of hospitalization in selected subjects.[5] Cur-

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The authors have disclosed no conflicts of interest.

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rently, NIV is the first-line method of ventilatory support for hypercapnic respiratory failure secondary to exacerbations of COPD or cardiogenic pulmonary edema.[6-10] Although the role of NIV in acute hypoxemic respiratory failure (AHRF) caused by various diseases is controversial, it has been shown by several randomized controlled trials (RCTs) and a systematic review that CPAP via NIV reduces the rate of endotracheal intubation, ICU stay, and ICU mortality.[8,11,12]

However, NIV failure has been reported to occur in 10–40% of subjects treated for ARF.[13,14] The main reason for this outcome has been suggested to be interface intolerance due to mask discomfort, tightened straps, and/or excessive air leaks.[15] Furthermore, NIV failure is strongly associated with worse outcome.[16] To increase treatment success rates, patient comfort should be an important goal of therapy.

In recent years, a new respiratory support therapy has been introduced. High-flow nasal cannula (HFNC) therapy allows the delivery of heated and humidified gas at up to 60 L/min via a wide-bore nasal cannula. Although there have been few reports showing the effectiveness of this device in adults, HFNC has been shown to improve dyspnea, breathing frequency, and oxygenation of subjects with ARF in several small observational trials.[17,18] In more recent years, 2 RCTs demonstrated the clinical efficacy of HFNC for subjects post-extubation and with acute lung injury.[19,20]

Since June 2012, we have been using HFNC for AHRF subjects with NIV intolerance. To demonstrate the benefits of this strategy, we retrospectively compared the outcomes among AHRF admissions at our hospital during the periods before and after the introduction of HFNC.

QUICK LOOK

Current knowledge

Heated and humidified high-flow nasal oxygen reduces ventilatory requirements by washing out the dead space of the upper airway and improves oxygenation by meeting patient inspiratory demands with a high F_{IO_2}. A small amount of end-expiratory pressure may also be observed, further improving oxygenation. Gas delivered at body temperature and 100% relative humidity allows high flows without discomfort associated with cool dry gas.

What this paper contributes to our knowledge

Using a retrospective analysis with historical controls, the use of high-flow nasal oxygen in a group of subjects with hypoxemic respiratory failure was associated with a reduction in the requirement for both invasive and noninvasive ventilation (NIV). High-flow nasal oxygen was a useful alternative to NIV in subjects with mask intolerance.

Methods

Setting and Study Design

We conducted a retrospective single-center cohort study to evaluate AHRF subjects requiring any respiratory support (invasive ventilation, NIV, or HFNC) who were consecutively admitted to our hospital between June 2010 and May 2014. We compared two 2-y periods, before (June 2010 to May 2012) and after (June 2012 to May 2014) the introduction of HFNC (pre- and post-HFNC periods). The ethics committee of Kobe City Medical Center General Hospital approved the study. Because this was a retrospective observational cohort study and included no therapeutic intervention, written informed consent was waived.

Subjects

Among all patients who required emergent admission to the respiratory care department at our hospital during the 2 study periods, we extracted the records of subjects with ARF for screening (Fig. 1). Subjects who needed NIV or invasive ventilation before admission were excluded. We then excluded subjects if they had a neoplastic disease, required urgent airway management (namely, respiratory arrest, asphyxia, or massive hemoptysis), or were in a comatose state because they were not suitable for survival analysis or as HFNC candidates. Additionally, subjects with pneumothorax, massive pleural effusions, or pulmonary embolisms were excluded because prognosis would be independent of respiratory support. Subjects who were able to breathe without any respiratory support (invasive ventilation, NIV, or HFNC) during the first 24 h after admission were also excluded. Finally, subjects with hypercapnia ($P_{aCO_2} \geq 45$ mm Hg) and those for whom arterial blood gases were not assessed were excluded.

Measurements

We collected the subjects' baseline characteristics (age, sex, AHRF etiology, arterial blood gas data, [P_{aO_2}, and P_{aCO_2}]). We compared the in-hospital mortality of subjects during the 2 study periods as the primary outcome. We also compared ICU/intermediate care unit/hospital stay, number of subjects requiring mechanical ventilation (NIV or invasive ventilation) and invasive ventilation, and ventilator days and ventilator-free days up to day 28 as the secondary outcomes. We defined ventilator-free days as the number of days subjects were alive and free from

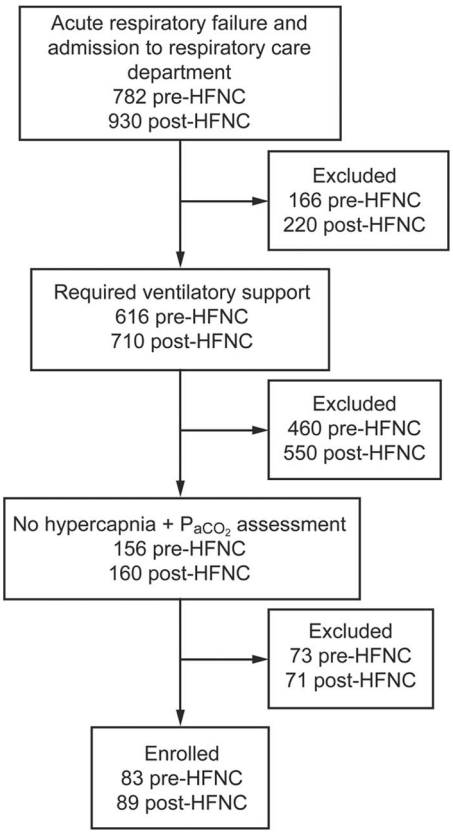

Fig. 1. Subject enrollment. Diseases not suitable for survival analysis or for high-flow nasal cannula (HFNC), the prognosis of which would be independent of respiratory support, were excluded.

mechanical ventilation, including both invasive ventilation and NIV up to day 28 of hospitalization.

Definitions

We defined ARF as the presence of both clinical signs and symptoms of acute respiratory distress (dyspnea, breathing frequency $\geq$ 30 breaths/min, use of accessory respiration muscles, presence of paradoxical breathing) and need for supplemental oxygenation to maintain a P_{aO_2} of $>$ 60 mm Hg or an S_{pO_2} of $>$ 90% on admission. For subjects with chronic respiratory failure, we enrolled those who needed more oxygen than usual to maintain a P_{aO_2} of $>$ 60 mm Hg or an S_{pO_2} of $>$ 90%. The type of respiratory support was categorized within 3 groups: invasive ventilation, NIV, and HFNC. Cases in which mechanical ventilatory support was used were defined as invasive ventilation. Cases in which NIV was used without switching to invasive ventilation (NIV failure) were defined as NIV. Cases in which HFNC was used without switching to NIV or invasive ventilation (HFNC failure) or in which NIV was initiated and switched to HFNC within 24 h were defined as HFNC. Cases in which NIV was used for $>$ 24 h and then switched to HFNC in the weaning process were also defined as NIV. AHRF etiology was classified in 4 groups: pneumonia (aspiration and other pneumonia, including bacterial, viral, and fungal), interstitial pneumonia, COPD and asthma, and others, such as ARDS, alveolar hemorrhage, congestive heart failure, and their coexistence.

Application and Setting of NIV and HFNC

In both periods, we used NIV as the first-line respiratory support for subjects with ARF who needed mechanical ventilation as long as they had no contraindications for NIV, such as respiratory arrest, improper mask fit, hypotensive shock, and urgent need for airway management.[4] As for AHRF, the need for mechanical ventilation was defined as clinical signs and symptoms of acute respiratory distress and an inability to maintain arterial blood gases with a P_{aO_2} of $>$ 60 mm Hg or an S_{pO_2} of $>$ 90% on oxygen at $>$ 10 L/min using a conventional face-mask delivery system. The indication for invasive ventilation was based on criteria used in the literature, including contraindications for NIV and NIV failure.[21] In the post-HFNC period, we used HFNC for subjects with AHRF who needed mechanical ventilation (as described above), who were NIV-intolerant, or who did not require invasive ventilation.

HFNC therapy was delivered using an Optiflow system (Fisher & Paykel Healthcare, Auckland, New Zealand) using a large-bore bi-nasal prongs. Flow was set to 35–45 L/min, and the F_{IO_2} was determined by the bedside clinician to maintain an S_{pO_2} of $>$ 90%. NIV was administered using a V60 noninvasive ventilator (Philips Respironics, Murrysville, Pennsylvania), and the NIV mask was the standard reusable oronasal mask used routinely at our hospital (ComfortFull [Philips Respironics] or RT040 [Fisher & Paykel Healthcare]). Inspiratory and expiratory pressures were titrated by the clinician.

Statistical Analysis

Continuous variables with normal distribution are expressed as mean $\pm$ SD, and variables with non-parametric distribution are presented as the median (interquartile range). Categorical variables are presented as *n* (%). The Student *t* test or Mann-Whitney *U* test was used to assess differences between the 2 periods according to their distribution. For categorical variables, we used the chi-square test. We used Kaplan-Meier curves to assess the time spent receiving mechanical ventilation, and the differences were examined by the log-rank test. $P < .05$ was considered statistically significant. We conducted

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Table 1. Number of Subjects per Type of Respiratory Support Administered

Respiratory Support	Pre-HFNC Period (June 2010 to May 2012) ($n = 83$)	Post-HFNC Period (June 2012 to May 2014) ($n = 89$)
Invasive ventilation, *n*	18	13
Invasive ventilation (first-line respiratory support)	3	3
NIV switch to invasive ventilation (NIV failure)	15	10
NIV, *n*	65	43
NIV (first-line respiratory support without switching to invasive ventilation)	65	40
HFNC switch to NIV (HFNC failure)		3
HFNC (without switching to NIV or invasive ventilation), *n*		33

Subjects were categorized into 3 groups: invasive ventilation, noninvasive ventilation (NIV), and high-flow nasal cannula (HFNC).

Table 2. Baseline Characteristics of Subjects in the 2 Study Periods

Characteristic	Pre-HFNC Period			Post-HFNC Period			
	NIV	Invasive Ventilation	Total	HFNC	NIV	Invasive Ventilation	Total
Subjects, *n*	65	18	83	33	43	13	89
Age, mean ± SD y	71.8 ± 15.5	70.4 ± 14.9	71.5 ± 15.3*	75.5 ± 9.6	77.6 ± 8.8	70.5 ± 11.7	75.8 ± 9.8*
Male, *n* (%)	45 (69)	10 (56)	55 (66)*	30 (91)	33 (77)	11 (85)	74 (83)*
P_{aO_2}/F_{IO_2}, mean ± SD	149 ± 60	130 ± 45†	145 ± 58‡	157 ± 41	154 ± 57	123 ± 42†	151 ± 51‡
Diagnosis, *n* (%)							
Pneumonia	35 (54)	11 (61)	46 (55)	15 (45)	31 (72)	9 (69)	55 (62)
Aspiration pneumonia	8 (12)	2 (11)	10 (12)	5 (15)	8 (19)	3 (23)	16 (18)
Other pneumonia	27 (42)	9 (50)	36 (43)	10 (30)	23 (53)	6 (46)	39 (44)
Interstitial pneumonia	17 (26)	2 (11)	19 (23)	13 (39)	4 (9)	1 (8)	18 (20)
COPD and asthma	4 (6)	0 (0)	4 (5)	1 (3)	4 (9)	0 (0)	5 (6)
Others	9 (14)	5 (28)	14 (17)	4 (12)	4 (9)	3 (23)	11 (12)

* Subject age and proportion of males were significantly higher in the post-high-flow nasal cannula (HFNC) period ($P < .05$).
† In each period, P_{aO_2}/F_{IO_2} of the subjects treated with invasive ventilation was significantly lower compared with noninvasive ventilation (NIV) or HFNC ($P < .05$).
‡ P_{aO_2}/F_{IO_2} was similar between the pre- and post-HFNC periods ($P = .5$).

statistical analyses using JMP 8 (SAS Institute, Cary, North Carolina).

Results

Subject Characteristics

In total, 83 subjects identified from 782 pre-HFNC records and 89 subjects from 930 post-HFNC records were included in the analysis (Table 1). In the pre-HFNC period, NIV and invasive ventilation were administered to 65 (78%) and 18 (22%) subjects, respectively. Conversely, in the post-HFNC period, HFNC was administered to 33 (37%) subjects, and NIV and invasive ventilation were administered to 43 (48%) and 13 (15%) subjects, respectively. In each period, 15 and 13 subjects experienced failure of the first-line respiratory support, respectively.

Baseline characteristics of the subjects in the 2 study periods are summarized in Table 2. Age and proportion of males were significantly higher in the post-HFNC period ($P < .05$). P_{aO_2}/F_{IO_2} was similar between pre- and post-HFNC periods ($P = .5$). In each period, P_{aO_2}/F_{IO_2} of the subjects treated with invasive ventilation was significantly lower compared with NIV or HFNC ($P < .05$). In both periods, pneumonia was the primary etiology causing AHRF. There was no significant difference in the rate of etiologies between each period (pneumonia: 55% vs 62%, interstitial pneumonia: 23% vs 20%, COPD and asthma: 5% vs 6%, and others: 17% vs 12%; $P = .2$).

In-Hospital Mortality Rate

Tables 3 and 4 present the in-hospital mortality rate for each etiology and each type of respiratory support, respectively. Overall, the in-hospital mortality rate was similar, although there was a non-significant and slight decrease from 35 to 27% ($P = .26$). Additionally, in-hospital mortality rates did not decrease significantly for any etiology.

Table 3. In-Hospital Mortality Rates in the 2 Study Periods

	Pre-HFNC Period	Post-HFNC Period	*P*
Overall in-hospital mortality rate, *n*/total *N* (%)	29/83 (35)	24/89 (27)	.26
Pneumonia	11/46 (24)	12/55 (22)	.80
Aspiration pneumonia	3/10 (30)	2/16 (13)	.27
Other pneumonia	8/36 (22)	10/39 (26)	.73
Interstitial pneumonia	14/19 (74)	8/18 (44)	.07
COPD and asthma	0/4 (0)	0/5 (0)	NA
Others	4/14 (29)	4/11 (36)	.68

HFNC = high-flow nasal cannula
NA = not assessed

Table 4. Outcomes for Each Type of Respiratory Support in the 2 Study Periods

Outcome	Pre-HFNC Period			Post-HFNC Period			
	NIV (*n* = 65)	Invasive Ventilation (*n* = 18)	Total (*n* = 83)	HFNC (*n* = 33)	NIV (*n* = 43)	Invasive Ventilation (*n* = 13)	Total (*n* = 89)
In-hospital mortality rate, %	35	33	35	18	30	38	27
ICU/IMCU stay, median (IQR), d	5 (3–9)	15.5 (7–24)	7 (3–10)	6 (4–12)	4 (3–11)	13 (4.5–29)	6 (3.5–12.5)
Hospital stay, median (IQR), d	15 (8.5–20)	26 (11–41.5)	16 (9–26)	22 (14–31.5)	13 (9–26)	25 (12–44)	17 (10.5–30)
Ventilator-free days up to day 28, median (IQR)	21 (0–26)	7 (0–22)	18 (0–25)	27 (27–28)	26 (17–26)	19 (0–25)	26 (20–27)

HFNC = high-flow nasal cannula
NIV = noninvasive ventilation
IMCU = intermediate care unit
IQR = interquartile range.

Table 5. Secondary Outcomes in the 2 Study Periods

Secondary Outcome	Pre-HFNC Period	Post-HFNC Period	*P*
ICU/IMCU stay, median (IQR), d	7 (3–10)	6 (3.5–12.5)	.80
Hospital stay, median (IQR), d	16 (9–26)	17 (10.5–30)	.33
Subjects requiring mechanical ventilation (NIV or invasive ventilation), *n* (%)	83 (100)	56 (63)	< .01
Subjects requiring invasive ventilation, *n* (%)	18 (22)	13 (15)	.22
Ventilator days, median (IQR)	5 (2–11)	2 (1–5)	< .05
Ventilator-free days up to day 28, median (IQR)	18 (0–25)	26 (20–27)	< .01

HFNC = high-flow nasal cannula
IMCU = intermediate care unit
NIV = noninvasive ventilation
IQR = interquartile range.

The difference was not assessed for COPD and asthma because none of the subjects died.

Secondary Outcomes

Table 5 presents ICU/intermediate care unit/hospital stay, number (%) of subjects requiring mechanical ventilation and invasive ventilation, and ventilator days and ventilator-free days up to day 28. There were no significant differences in ICU, intermediate care unit ($P = .80$), and hospital ($P = .33$) stay. In the post-HFNC period, significantly fewer subjects required mechanical ventilation (NIV or invasive ventilation) (100% vs 63%, $P < .01$), although there was no significant difference in subjects requiring invasive ventilation (22% vs 15%, $P = .22$). Additionally, there were significantly fewer ventilator days (median [in-

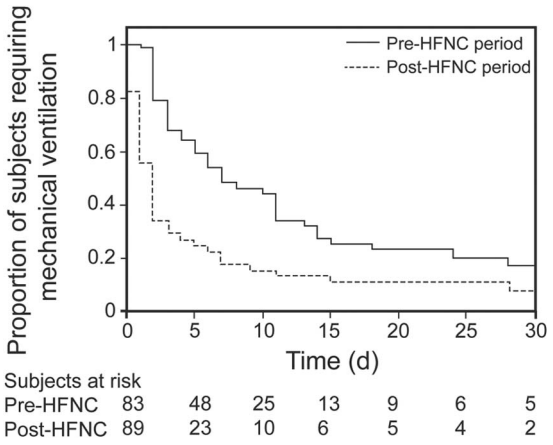

Fig. 2. Proportion of subjects receiving mechanical ventilation (noninvasive or invasive ventilation). HFNC = high-flow nasal cannula.

terquartile range] of 5 [2–11] vs 2 [1–5] d, $P < .05$) and more ventilator-free days up to day 28 (median [interquartile range] of 18 [0–25] vs 26 [20–27] d, $P < .01$). A comparison of the 2 curves of the proportion of subjects receiving mechanical ventilation (NIV or invasive ventilation) showed the same significant difference ($P < .01$) (Fig. 2). Table 4 shows the outcomes for each type of respiratory support in the 2 study periods.

Discussion

The study showed that the introduction of HFNC decreased ventilator use (including invasive ventilation and NIV) without affecting mortality or ICU/intermediate care unit/hospital stay. Our results also validated our strategy of using HFNC to treat subjects with AHRF. To date, few data are available on the clinical impact of HFNC.

Although HFNC is a new device that was recently introduced, its use has increased rapidly. In addition to washout of the pharyngeal dead space, decrease in inspiratory resistance, and supply of adequately warmed and humidified gas, HFNC has been shown to provide low levels of positive airway pressure, which is suspected to contribute to improving oxygenation and decreasing breathing effort.[22-24] Despite this physiological evidence, there are limited published studies on HFNC use in adults with ARF. Roca et al[25] were the first to show the clinical benefit of HFNC in ARF by presenting significant improvement in both clinical and physiological parameters after 30 min of HFNC compared with face-mask oxygen therapy. Sztrymf et al[17,26] also demonstrated the physiological benefits of HFNC compared with face-mask oxygen therapy in retrospective observational studies. Parke et al[27] conducted a prospective randomized comparative study of mild-to-moderate AHRF and showed that more subjects with HFNC succeeded with their allocated therapy compared with face-mask oxygen therapy. Maggiore et al[19] demonstrated that HFNC resulted in a lower re-intubation rate compared with an air-entrainment mask in an RCT with subjects post-extubation. These results suggest some clinical efficacy of HFNC in the treatment of AHRF. However, there is a paucity of clinical trial data on HFNC compared with other respiratory support, such as NIV and invasive ventilation, which are the main respiratory support modalities for severe AHRF. A large RCT (FLORALI [High-Flow Nasal Oxygen Therapy in Resuscitation of Patients With Acute Lung Injury] study) demonstrating that HFNC resulted in lower mortality rates compared with oxygen therapy or NIV was recently completed.[20] Still, there were no previously published clinical studies evaluating the beneficial effect associated with the introduction of HFNC. Therefore, our study provides some new information about the impact and strategy of HFNC use.

For patients with severe AHRF who do not respond to standard oxygen therapy, NIV is applied as the first-line treatment if there is no urgent need for intubation.[25] However, NIV failure has been experienced often because of mask intolerance or inadequate cooperation.[4] Before the introduction of HFNC, we had few alternatives for managing those patients, and sedation,[28] switch to invasive ventilation,[29] or provision of standard oxygen therapy as a ceiling treatment was often necessary. In the post-HFNC period, however, we have used HFNC for these patients in our clinical practice. In our study, 38% (33/86) of subjects met the criteria for HFNC and were NIV-intolerant. Notably, in the pre-HFNC period, 19% (15/80) of subjects experienced NIV failure, a rate similar to previously reported rates (10–40%).[13,14] One possible explanation for the different failure rates between the 2 periods is that in the pre-HFNC period, we continued to use NIV even when subjects needed sedatives. Another explanation is that subjects were older in the post-HFNC period than in the pre-HFNC period, which might lead to more NIV failure. We evaluated the impact of HFNC, and our results indicated that this strategy was safe and effective in clinical practice.

Our study has several limitations. First, because this was a retrospective historical control study, it was not possible to elucidate some confounding factors, such as changes in the number of subjects, treatment, and staff members, which might have influenced the results. Second, our subjects were carefully selected from the total population using strict criteria. Although this means that the prognosis of our subjects could be influenced by the type of respiratory support, the conclusion cannot be applied to subjects with the conditions and statuses excluded from this study. Third, despite the potential benefit of the HFNC strategy, our results should not be overinterpreted. Our candidates for HFNC therapy were only subjects who presented with NIV intolerance. At present, NIV remains the first-line treatment for severe AHRF. However, although a recent RCT showed that HFNC resulted in lower

mortality rates compared with NIV,[20] the benefits of HFNC should be validated in future trials. Fourth, although all clinicians were encouraged to use the criteria for invasive ventilation, NIV, and HFNC by uniform protocol within our department, the decision was dependent on attending clinicians, and the criteria were subjective in part. As it was easier for clinicians to begin respiratory support with HFNC, it might be possible that less severe subjects who could not tolerate NIV were treated with HFNC. Thus, this might be the cause of the higher rate of NIV intolerance in the post-HFNC period. Fifth, we did not measure delivered F_{IO_2}; this parameter might differ based on the flow setting during HFNC and the subjects' inspiratory flow. Finally, the small number of subjects limits the reliability of our results.

Conclusions

Our HFNC strategy was found to be effective, and HFNC can be used as an alternative to NIV in AHRF subjects with NIV intolerance. However, generalizing this finding to all types of respiratory failure would be premature, as our subjects were highly selected. Further studies are needed to conclusively demonstrate the efficacy of HFNC.

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