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Sequential Application of Oxygen Therapy Via High-Flow Nasal Cannula and Noninvasive Ventilation in Acute Respiratory Failure: An Observational Pilot Study

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BACKGROUND: The aim of this study was to evaluate the clinical efficacy of humidified oxygen via high-flow nasal cannula (HFNC) alternating with noninvasive ventilation (NIV) in acute hypoxemic respiratory failure (AHRF). METHODS: We performed a prospective observational study in a 12-bed ICU of a university hospital. All subjects with a P_{aO_2}/F_{IO_2} of ≤ 300 mm Hg with standard mask oxygen and a breathing frequency of > 30 breaths/min or signs of respiratory distress were included and treated with HFNC first and then NIV. Ventilatory parameters, blood gases, and tolerance were recorded during 2 consecutive sessions of NIV and HFNC. Outcome was assessed after continuation of this noninvasive strategy. RESULTS: Twenty-eight subjects with AHRF were studied, including 23 (82%) with ARDS. Compared with standard oxygen therapy, P_{aO_2} significantly increased from 83 (68–97) mm Hg to 108 (83–140) mm Hg using HFNC and to 125 (97–200) mm Hg using NIV ($P < .01$), whereas breathing frequency significantly decreased. HFNC was significantly better tolerated than NIV, with a lower score on the visual analog scale. The nonintubated subjects received HFNC for 75 (27–127) h and NIV for 23 (8–31) h. Intubation was required in 10 of 28 subjects (36%), including 8 of 23 subjects with ARDS (35%). After HFNC initiation, a breathing frequency of ≥ 30 breaths/min was an early factor associated with intubation. CONCLUSIONS: HFNC was better tolerated than NIV and allowed for significant improvement in oxygenation and tachypnea compared with standard oxygen therapy in subjects with AHRF, a large majority of whom had ARDS. Thus, HFNC may be used between NIV sessions to avoid marked impairment of oxygenation. *Key words: acute respiratory failure; acute respiratory distress syndrome (ARDS); noninvasive ventilation; nasal high-flow oxygen therapy; intensive care unit (ICU).* [Respir Care 2015;60(2):1–•. © 2015 Daedalus Enterprises]

Introduction

The use of noninvasive ventilation (NIV) as first-line ventilatory support is well established in patients with a severe exacerbation of COPD[1,2] and cardiogenic pulmonary edema.[3] By contrast, conflicting results exist regarding its use in patients with de novo acute hypoxemic respiratory failure (AHRF). Indeed, NIV is more likely to fail in hypoxemic patients,[4] and the rate of intubation could reach 60% in unselected patients admitted to ICUs for

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AHRF.[5,6] Despite these concerns, surveys show that NIV is initiated as first-line ventilatory support in 20–30% of subjects with AHRF.[4,6] NIV has even been used in patients with ARDS.[7,8] However, these patients required prolonged NIV sessions, and poor tolerance to NIV was the reason for intubation in 5–25% of the cases in hypoxemic patients.[7,9-11] In a prospective cohort study, poor tolerance was independently associated with an increased risk of intubation.[4] In case of discomfort, the switch from NIV to standard oxygen therapy could lead to oxygenation impairment and subsequently to endotracheal intubation.

Humidified oxygen therapy via high-flow nasal cannula (HFNC) is a recently available technique delivering a high flow of heated and humidified oxygen through simple nasal prongs. It has been shown that HFNC can help generate low levels of CPAP due to the high flow of fresh gas,[12] improve comfort and oxygenation, and attenuate signs of respiratory distress compared with standard oxygen therapy.[13,14] Therefore, HFNC coupled to NIV could be a way to limit prolonged NIV sessions by maintaining adequate oxygenation between them. The aim of our study was to assess comfort, ventilatory parameters, and oxygenation in subjects with AHRF treated consecutively with HFNC and NIV.

QUICK LOOK

Current knowledge

Heated and humidified high-flow oxygen via nasal cannula improves oxygenation by meeting patient inspiratory flow demand and providing a small positive airway pressure. Minute ventilation requirements are also reduced by washout of the upper airway anatomic dead space.

What this paper contributes to our knowledge

In a small group of subjects with acute hypoxemic respiratory failure, heated and humidified high-flow oxygen by nasal cannula and noninvasive ventilation (NIV) were superior to standard oxygen therapy with respect to oxygenation and ventilatory requirement. High-flow nasal oxygen was better tolerated than NIV with better subject-reported comfort. One-third of all subjects required intubation.

Methods

We conducted a prospective observational pilot study in a 12-bed medical ICU at the University Hospital of Poitiers in France between January 2010 and February 2011. The study protocol was approved by the local research ethics committee of the Jean Bernard University Hospital in Poitiers.

Subjects

All subjects with de novo AHRF were included if they met both of the following criteria: (1) a breathing frequency of > 30 breaths/min or clinical signs of respiratory distress, (2) a P_{aO_2}/F_{IO_2} of ≤ 300 mm Hg after spontaneously breathing oxygen at 15 L/min for > 15 min through a non-rebreathing face mask (Hudson RCI/Teleflex Medical, High Wycombe, United Kingdom). Baseline-delivered F_{IO_2} was measured with a portable oxygen analyzer (MX300, Teledyne Analytical Instruments, City of Industry, California), inserted in a conventional face mask delivering oxygen therapy during spontaneous breathing. We excluded subjects who had underlying chronic respiratory disease, cardiogenic pulmonary edema, or aplasia; subjects with altered consciousness defined by a Glasgow coma score of ≤ 12 points or hemodynamic instability defined by systolic arterial blood pressure < 90 mm Hg, mean arterial blood pressure < 65 mm Hg, or vasopressor use; and subjects who needed immediate endotracheal intubation. Subjects who met inclusion criteria were consequently included and treated by HFNC followed by NIV.

Adjustments of NIV and HFNC

After inclusion, subjects were treated successively first with a 2-h session of HFNC and then with a 1-h session of NIV. Sequential application of these 2 treatments was repeated to deliver 16 h of HFNC and 8 h of NIV per d (Fig. 1).

The HFNC device (Optiflow, Fisher & Paykel Healthcare, Auckland, New Zealand) includes an air-oxygen blender, which allows the accurate adjustment of F_{IO_2} between 0.21 and 1.0 and delivery of gas flow up to 70 L/min through a heated humidifier (MR850, Fisher & Paykel Healthcare). The gas mixture was routed through a circuit to the subject at a temperature of 37°C and an absolute humidity of 44 mg/L via large-bore bi-nasal prongs. HFNC was initially administered at a gas flow of 50 L/min and a F_{IO_2} of 1.0. F_{IO_2} was adjusted to maintain an S_{pO_2} of $> 92\%$. Blood gases were measured within 1 h after HFNC initiation.

NIV was delivered to the subject in a semirecumbent position with a full-face mask (Fisher & Paykel Health-

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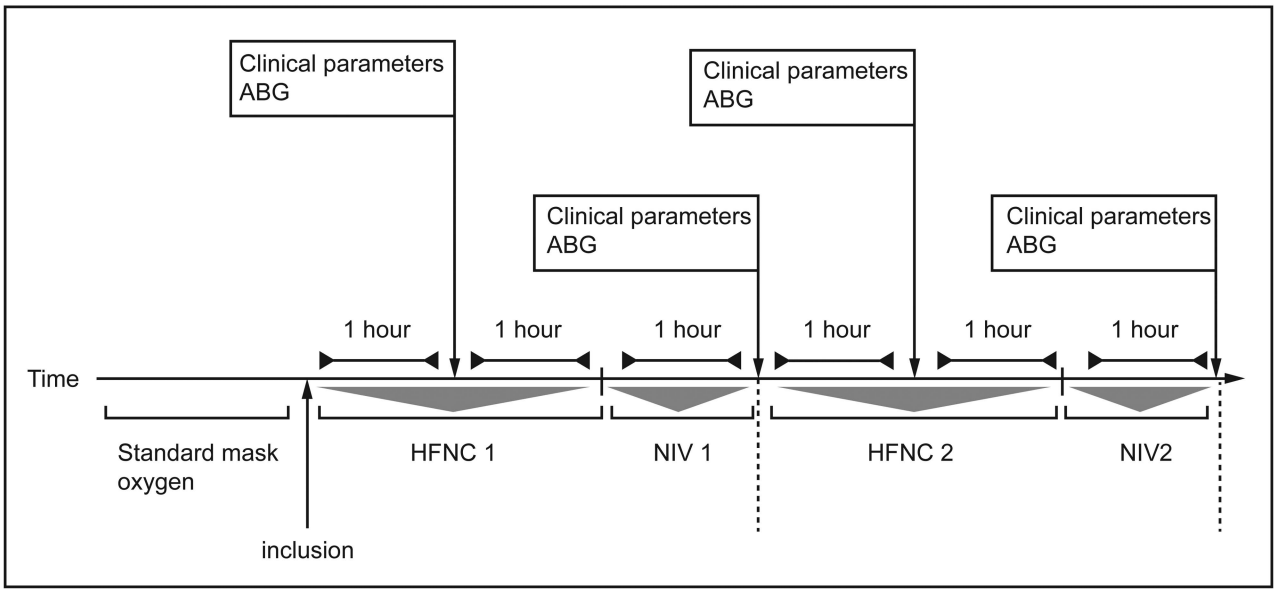

Fig. 1. Design of the study. After inclusion, subjects were treated successively first with a 2-h session of oxygen via high-flow nasal cannula (HFNC) and then with a 1-h session of noninvasive ventilation (NIV). Sequential application of these 2 treatments was repeated to deliver 16 h of HFNC and 8 h of NIV per d. Respiratory parameters, ventilatory settings, tolerance, F_{IO_2}, and arterial blood gases (ABG) were recorded at baseline during spontaneous ventilation with a conventional face mask and 1 h after initiation of HFNC and NIV. These variables were recorded again during the second session of HFNC and NIV.

care) connected to an ICU ventilator with a dedicated NIV mode (Evita XL, Evita 4, or Evita 2 dura, Dräger, Lübeck, Germany) equipped with a heated humidifier (MR850, Fisher & Paykel Healthcare). Subjects were ventilated by NIV with a pressure support level targeting an expired tidal volume of 6–8 mL/kg and a breathing frequency of < 30 breaths/min. F_{IO_2} was adjusted to maintain S_{pO_2} at $> 92\%$ with PEEP of at least 4 cm H_2O.

Data Collection

Subjects' characteristics, including etiology of acute respiratory failure, clinical criteria for ARDS, and severity score, were prospectively recorded. The severity of ARDS was stratified using the recent Berlin definition,[15] according to the value of oxygenation recorded within the first hour after NIV initiation, and classified as mild ($201 \leq P_{aO_2}/F_{IO_2} \leq 300$ mm Hg), moderate ($101 \leq P_{aO_2}/F_{IO_2} \leq 200$ mm Hg), or severe ($P_{aO_2}/F_{IO_2} \leq 100$ mm Hg). Respiratory parameters, ventilatory settings, tolerance, F_{IO_2}, and blood gases were recorded at baseline during spontaneous ventilation with a conventional face mask and 1 h after initiation of HFNC and NIV. Tolerance was measured using an unmarked 100-mm visual analog scale that had ends marked with "no constraint" and "intolerable." All these variables were recorded 1 h after initiation of the second session of HFNC and NIV. The noninvasive strategy using NIV and HFNC between NIV sessions was continued until regression of respiratory distress or intubation occurred.

The following criteria were used for endotracheal intubation: loss of consciousness or psychomotor agitation hindering nursing care; persistent hypotension (defined by systolic arterial blood pressure < 90 mm Hg or mean arterial blood pressure < 65 mm Hg) despite fluid resuscitation or need for vasopressors; or 2 of the following criteria: evident worsening of respiratory distress, breathing frequency of > 40 breaths/min, abundant secretions, S_{pO_2} remaining below 92% despite an F_{IO_2} of 1.0, or pH < 7.35. NIV failure was defined by the need for endotracheal intubation.

Statistical Analysis

All data are expressed as mean ± SD or as median and interquartile ranges (25th and 75th percentiles), and dichotomous variables are reported as number (percentage). Given the small sample of subjects, we used non-parametric tests. Qualitative data were compared using the Fisher exact test, and quantitative data were compared by one-way analysis of variance (Friedman test) for repeated measures or using the Wilcoxon signed-rank test. $P < .05$ was considered statistically significant. Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, North Carolina).

A receiver operating characteristic curve was plotted to determine the threshold value of breathing frequency at

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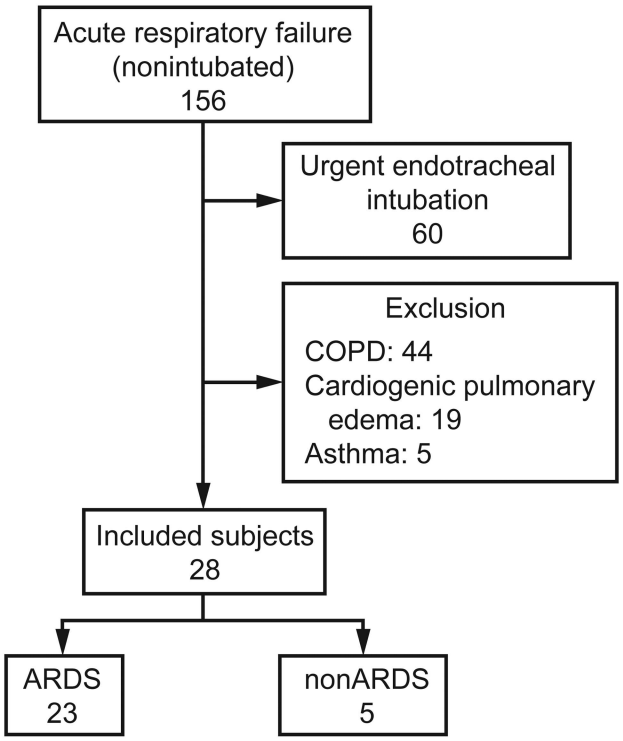

Fig. 2. Flow chart of the study.

the end of the first HFNC period, which provided a prediction of intubation with the best sensitivity and specificity.

Results

After exclusion of subjects who required immediate endotracheal intubation and those with chronic pulmonary disease or cardiogenic pulmonary edema, 28 of 156 subjects admitted in our ICU for respiratory distress were included (Fig. 2). Among them, 23 (82%) met clinical criteria for ARDS, with a P_{aO_2}/F_{IO_2} median at NIV initiation of 169 (169–216). Eight subjects were classified as mild ARDS, 14 subjects as moderate ARDS, and one subject as severe ARDS. The characteristics of the subjects at inclusion are shown in Table 1.

At inclusion, median F_{IO_2} measured through the nonrebreathing face mask was 0.63 (0.62–0.63) using an oxygen flow of 15 (15–15) L/min. Ventilatory settings adjusted during NIV were a pressure support level of 13 (12–15) cm H_2O, PEEP of 4 (4–5) cm H_2O, and F_{IO_2} of 0.9 (0.6–1.0). During HFNC, F_{IO_2} was 1.0 (0.9–1.0), and fresh gas flow was 50 (50–50) L/min.

Comparison of Clinical Parameters and Oxygenation During Standard Oxygen Therapy, HFNC, and NIV

P_{aO_2} increased in 20 of 28 subjects after initiation of HFNC and was significantly higher during HFNC and NIV compared with standard oxygen therapy (Table 2 and Fig. 3). However, P_{aO_2}/F_{IO_2} increased only during NIV. Breathing frequency significantly decreased after initiation of HFNC, without further change throughout the ensuing HFNC/NIV sessions. Heart rate significantly decreased after initiation of HFNC and remained stable throughout the ensuing HFNC/NIV sessions.

HFNC was significantly better tolerated than NIV, with a lower score on the visual analog scale of 16 (3–46) mm versus 61 (41–84) mm ($P = .004$). Comfort tended to be better during the second session compared with the first session of NIV, but it was not significant, with a median score of 49 (14–84) mm ($P = .10$). No subject developed facial or nasal pressure sores, and no subject needed analgesia or sedation due to NIV intolerance.

Table 1. Subjects' Characteristics

Variables	Values
Age, median (IQR), y	61 (49–68)
Males/females, *n* (%)	20/28 (71)
BMI, median (IQR), kg/m^2	26 (23–31)
Immunosuppression, *n* (%)*	10 (36)
Etiology of AHRF, *n*/*n* total (%)	
Community-acquired pneumonia	13/28 (46)
Hospital-acquired pneumonia	5/28 (18)
Postoperative respiratory failure	3/28 (11)
Other†	7 (25)
At admission, median (IQR), points	
SAPS II	36 (27–41)
Glasgow coma scale	15 (15–15)
Breathing frequency, breaths/min	31 (27–37)
P_{aO_2}, mm Hg	83 (68–97)
F_{IO_2}, measured	0.63 (0.62–0.63)
Ventilatory settings and arterial blood gas at 1 h of NIV initiation, median (IQR)	
Pressure support, cm H_2O	13 (12–15)
PEEP, cm H_2O	4 (4–5)
F_{IO_2}	0.7 (0.6–1.0)
P_{aO_2}/F_{IO_2}	192 (158–251)
P_{aCO_2}, mm Hg	40 (33–48)
pH	7.43 (7.37–7.47)

* Immunosuppression included hematologic malignancy ($n = 5$), immunosuppressive therapy ($n = 4$), and acquired immune deficiency syndrome ($n = 1$).
† Other included ARDS secondary to acute pancreatitis, diffuse alveolar hemorrhage, chest trauma, and pulmonary embolism.
IQR = interquartile range
BMI = body mass index
AHRF = acute hypoxemic respiratory failure
SAPS II = Simplified Acute Physiology Score II
NIV = noninvasive ventilation

Outcome and Predictors of Intubation

Ten of 28 subjects with AHRF (36%) and 8 of 23 subjects with ARDS (35%) failed the HFNC/NIV strategy and

Table 2. Evolution of Arterial Blood Gases and Clinical Parameters in All Subjects During HFNC and NIV Sessions

Variables	Baseline	HFNC 1	NIV 1	HFNC 2	NIV 2
P_{aO_2}, mm Hg	83 (68–97)	108 (83–140)*	125 (97–200)*	95 (75–116)†	121 (101–190)*
F_{IO_2}	0.63 (0.62–0.63)	1.0 (0.95–1.0)*	0.7 (0.6–1.0)	1.0 (0.6–1.0)*	0.7 (0.6–0.8)
P_{aO_2}/F_{IO_2}, mm Hg	132 (119–163)	127 (98–166)	192 (158–251)*‡	128 (83–188)	187 (155–245)*‡§
P_{aCO_2}, mm Hg	38 (33–46)	38 (33–45)	40 (33–48)	41 (32–46)	40 (34–49)
pH	7.43 (7.38–7.48)	7.42 (7.37–7.47)	7.43 (7.37–7.47)	7.42 (7.37–7.47)	7.40 (7.38–7.47)
Visual analog scale (0 mm = no constraint, 100 mm = intolerable), mm	NA	16 (3–46)§	61 (41–84)	18 (4–31)§	49 (14–61)
Heart rate, beats/min	102 (95–122)	98 (92–112)†	94 (78–109)†	87 (78–106)†	89 (76–108)†
Systolic arterial pressure, mm Hg	133 (121–145)	123 (105–143)	126 (111–153)	126 (117–139)	137 (125–148)

All variables are expressed as median and interquartile range (25th and 75th percentiles).
* $P < .01$ versus baseline values.
† $P < .05$ versus baseline values.
‡ $P < .01$ versus high-flow nasal cannula (HFNC) values.
§ $P < .01$ versus the visual analog scale score for noninvasive ventilation (NIV) intolerance.
NA = not applicable

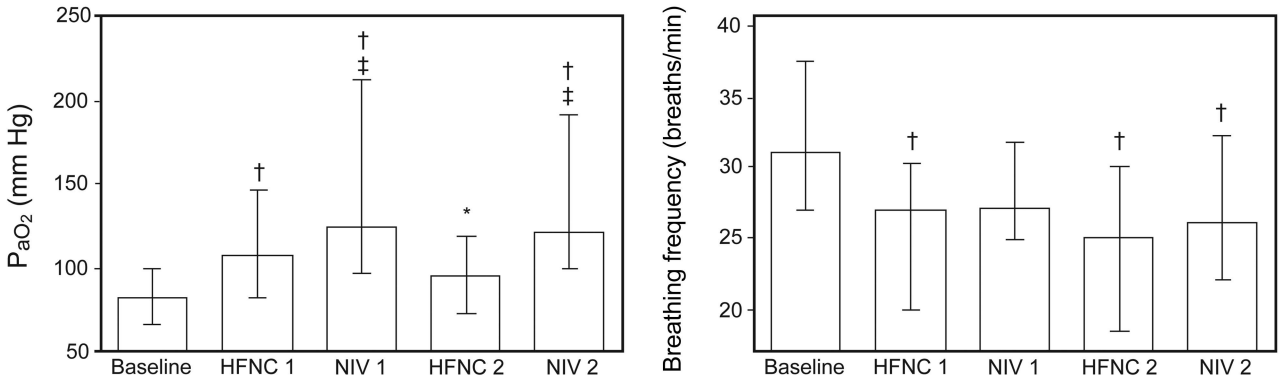

Fig. 3. Evolution of P_{aO_2} and breathing frequency in all subjects from baseline to the end of both oxygen therapy via high-flow nasal cannula (HFNC) and noninvasive ventilation (NIV). P_{aO_2} increased significantly from baseline to HFNC or NIV sessions ($P < .001$). Frequency decreased significantly form baseline to HFNC or NIV sessions ($P = .003$). * $P < .05$ vs baseline; † $P < .01$ vs baseline; ‡ $P < .01$ vs HFNC. Data are expressed as mean ± SD.

were subsequently intubated (Table 3). The median time between admission and endotracheal intubation was 30 (20–36) h (Fig. 4). The reasons for endotracheal intubation were worsening of respiratory distress ($n = 7$), shock ($n = 2$), and respiratory arrest ($n = 1$). Subjects who required endotracheal intubation had a higher breathing frequency at baseline as well as at 1 h after initiation of the first HFNC session and at the end of the NIV sessions (Table 3). A breathing frequency of ≥ 30 breaths/min at 1 h after initiation of the first HFNC session allowed for discrimination between intubated and non-intubated subjects with a sensitivity of 94.1% and specificity of 87.5% (area under the receiver operating characteristic curve of 0.88) (Fig. 5). Only one of 8 subjects with a breathing frequency of ≥ 30 breaths/min underwent successful noninvasive strategy and did not require intubation. Overall, subjects received HFNC for 35 (23–103) h and NIV for 13 (6–30) h, whereas non-intubated subjects received HFNC for 75 (27–127) h and NIV for 23 (8–31) h.

Discussion

We report the clinical impact of alternating HFNC and NIV in subjects with AHRF, a large majority of whom met the clinical criteria for ARDS. HFNC was better tolerated than NIV; in comparison with standard oxygen therapy, it helped to improve oxygenation and to attenuate signs of respiratory distress. Tachypnea was the only predictive factor for intubation when this NIV strategy was applied.

Effects on Clinical Parameters, Oxygenation, and Comfort

In the literature, we found that HFNC improved oxygenation and attenuated signs of respiratory distress by

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Table 3. Comparison of Characteristics of Intubated and Non-Intubated Subjects

	Non-intubated (n = 18)	Intubated (n = 10)	P
Age, median (IQR), y	65 (51–71)	58 (47–63)	.29
Males, *n* (%)	14 (78)	6 (60)	.68
BMI, median (IQR), kg/m^2	27 (22–32)	26 (24–27)	.84
Immunosuppression, *n* (%)*	6/18 (33)	4/10 (40)	< .99
Etiology of AHRF, *n*/*n* total (%)			.49
Community-acquired or hospital-acquired pneumonia	11/18 (61)	7/10 (70)	
Postoperative respiratory failure	3/18 (17)	0	
Other†	4/18 (22)	3/10 (30)	
ARDS, *n* (%)	15 (83)	8 (80)	< .99
Mortality, *n*	0/18	2/10	.12
Total duration of mechanical ventilation, median (IQR), d	4 (2–5)	20 (17–26)‡	.001
ICU stay, median, (IQR), d	7 (5–10)	17 (12–24)‡	.002
At admission, median (IQR)			
SAPS II on admission	36 (27–39)	36 (29–43)	.75
Breathing frequency, breaths/min	29 (26–33)	39 (30–43)‡	.02
P_{aO_2}/F_{IO_2} measured at baseline, mm Hg	127 (110–136)	154 (121–164)	.33
P_{aCO_2}, baseline	39 (35–43)	33 (29–45)	.90
Ventilatory settings and respiratory parameters at 1 h of NIV initiation, median (IQR)			
Pressure support, cm H_2O	13 (12–15)	13 (12–15)	.58
PEEP, cm H_2O	4 (4–5)	4 (4–5)	.74
F_{IO_2}	0.7 (0.7–1.0)	0.7 (0.7–1.0)	.37
P_{aO_2}/F_{IO_2}	190 (190–238)	207 (207–275)	.71
P_{aCO_2}, mm Hg	40 (34–49)	36 (31–44)	.72
pH	7.42 (7.38–7.44)	7.44 (7.36–7.48)	.83
Breathing frequency, breaths/min	26 (26–28)	33 (33–34)	.02
HFNC setting and respiratory parameters at 1 h of initiation, median (IQR)			
Oxygen flow, L/min	50 (50–50)	50 (50–50)	.59
F_{IO_2}	1.0 (1.0–1.0)	1.0 (.01–1.0)	< .99
P_{aO_2}/F_{IO_2}, mm Hg	122 (122–158)	128 (128–182)	.60
P_{aCO_2}, mm Hg	41 (35–46)	36 (31–41)	.13
pH	7.41 (7.36–7.45)	7.46 (7.38–7.48)	.39
Breathing frequency, breaths/min	25 (25–27)	31 (31–33)‡	.003
Breathing frequency ≥ 30 breaths/min, *n* (%)	1 (5)	7 (70)‡	.001

* Immunosuppression included hematologic malignancy, immunosuppressive therapy, and acquired immune deficiency syndrome.
† Other included ARDS secondary to acute pancreatitis, diffuse alveolar hemorrhage, chest trauma, and pulmonary embolism.
‡ There were significant differences between non-intubated and intubated subjects.
IQR = interquartile range
BMI = body mass index
AHRF = acute hypoxemic respiratory failure
SAPS II = Simplified Acute Physiology Score II
NIV = noninvasive ventilation
HFNC = high-flow nasal cannula

decreasing breathing frequency in patients with AHRF.[13,14] These results had already been shown 30 min after initiation of HFNC,[13] with sustained respiratory improvement for up to 48 h compared with conventional oxygen therapy.[14] Our results were obtained with a more severely ill population of hypoxemic subjects, the majority of whom met the clinical criteria for ARDS. Compared with standard oxygen therapy, HFNC can improve oxygenation first by providing a better matching of gas flow in the case of high inspiratory flow, thereby ensuring higher F_{IO_2},[16] and second by generating low levels of PEEP that may increase end-expiratory lung volume.[12,17] We found that P_{aO_2} significantly increased during HFNC compared with oxygen therapy, whereas P_{aO_2}/F_{IO_2} remained similar, suggesting that oxygenation improvement was due more to increased F_{IO_2} than a previously described potential PEEP effect.[12] In contrast to previous studies[7,9,10,18] and probably due to our small sample of intubated subjects, P_{aO_2}/F_{IO_2} was not associated with an increased risk of intubation. In contrast, low breathing frequency at baseline and its early reduction at the end of HFNC sessions were indeed closely associated with the success of the strategy.

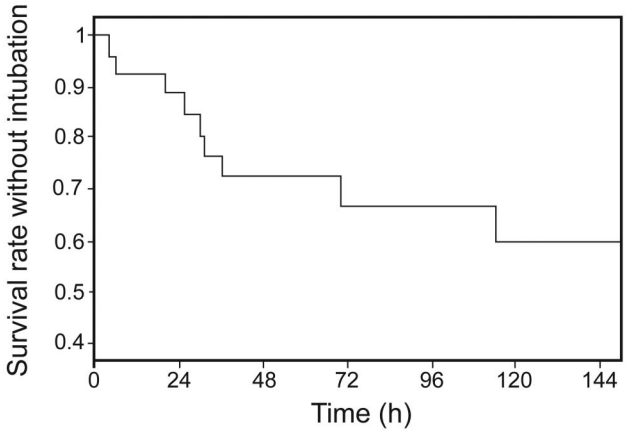

Fig. 4. Time to endotracheal intubation rate in all subjects.

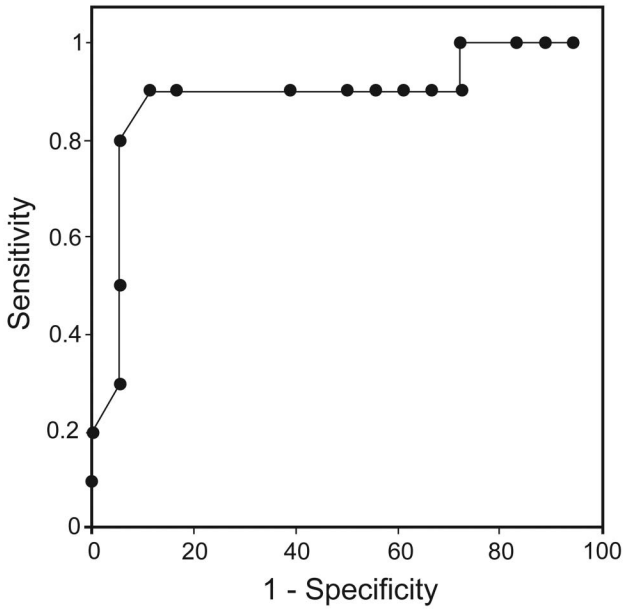

Fig. 5. The area under the receiver operating characteristic curve for breathing frequency at the end of the first HFNC period designed to discriminate intubated from non-intubated subjects was 0.88. The threshold frequency of 29 breaths/min allowed discrimination between intubated and non-intubated subjects with a sensitivity of 94.1% and specificity of 87.5%.

It has been found that patient comfort is higher with HFNC than with oxygen therapy.[13,14] Not surprisingly, we found that subjects' comfort was also higher during HFNC sessions compared with NIV sessions. Therefore, our strategy of combining NIV and HFNC was prolonged and applied continuously for $>$ 3 d in non-intubated subjects. Moreover, of the 10 subjects who failed NIV, none were intubated for intolerance to NIV. In the literature, poor NIV tolerance was the reason for intubation in 5%,[9] 9%,[10] and 14%[11] of subjects with AHRF and up to 25%[7] in subjects with ARDS. In the survey by Demoule et al,[4] good NIV tolerance was observed in only 7% of subjects who failed NIV and constituted an independent factor for NIV failure.

Intubation Rate

Our intubation rate of 36% is close to the 25–35% rate reported in randomized controlled trials evaluating NIV in AHRF.[11,19] However, in these 2 studies, nearly 20–30% of the subjects received NIV for cardiogenic pulmonary edema, a condition associated with a markedly lower intubation rate.[3] Moreover, subjects enrolled in such randomized studies are selected, whereas intubation rates up to 45–50% have been reported in a series of unselected subjects with AHRF of non-cardiac origin[8,9] and even up to 60% in prospective cohort studies.[5,6] In a recent study focusing on ARDS subjects receiving NIV as first-line therapy according to the Berlin ARDS classification, Thille et al[20] reported an intubation rate of 61%. These results compare favorably with the 35% intubation rate in our subjects meeting the clinical criteria for ARDS. In the largest study to date evaluating the impact of HFNC on the outcome of 38 subjects with AHRF, Sztrymf et al[14] reported an intubation rate of only 24%. However, the proportion of subjects meeting clinical criteria for ARDS was not mentioned. The mortality in our study was also particularly low compared with the literature.[15] However, our subjects were less severe, selected, and without other organ failure.

Clinical Implications and Limitations

The first limitation is that all subjects received standard oxygen and then HFNC followed by NIV without return to baseline with standard oxygen therapy. However, we observed a rapid reduction in breathing frequency when switching from standard oxygen to HFNC, and it is highly unlikely, given the high severity of our subjects, that the improvement was related to recovery from respiratory disease.

Another limit was the lack of a controlled group to assess the impact of the strategy combining HFNC with NIV on outcome. Such a multi-center randomized controlled study, called the FLORALI trial (NCT01320384), is currently ongoing.

The third and more important point is that benefits in terms of oxygenation were less pronounced during HFNC than during NIV. Nevertheless, the more severely ill subjects may require NIV for particularly prolonged sessions. In the study by Antonelli et al,[7] NIV was continuously applied for a median duration of 42 h. In their study, NIV was applied to 30% of subjects via a helmet, an interface that has previously exhibited higher tolerance than a face mask.[21,22] Yet, despite the relatively comfortable interface and the experience of a research team skilled in NIV, the rate

of intubation due to NIV intolerance reached 25%.[7] Given how difficult it is to maintain continuous and prolonged NIV sessions, we used HFNC as a bridge between them. This association enabled us to pursue the strategy without marked impairment of oxygenation between NIV sessions and with a relatively low intubation rate. However, it has been suggested that NIV may delay intubation and increase the mortality rate of patients with AHRF after NIV failure. [9] To avoid delaying intubation, we consequently used predetermined criteria for intubation, and NIV was never continued in the event of altered consciousness or shock. Although the use of sedation to continue NIV despite intolerance has been reported over recent years in small studies,[23–25] we did not give these medications.

Conclusions

Compared with standard oxygen therapy, HFNC had beneficial effects on oxygenation and respiratory distress symptoms in subjects with AHRF. Despite less oxygenation improvement compared with NIV, HFNC was better tolerated and may be used as a bridge between NIV sessions, with the aim of pursuing a coupled noninvasive strategy of ventilation without a marked impairment of oxygenation.

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