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Early high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure in the ED: A before-after study

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ABSTRACT

Objectives: To compare clinical impact after early initiation of high-flow nasal cannula oxygen therapy (HFNC) versus standard oxygen in patients admitted to an emergency department (ED) for acute hypoxemic respiratory failure.

Methods: We performed a prospective before-after study at EDs in two centers including patients with acute hypoxemic respiratory failure defined by a respiratory rate above 25 breaths/min or signs of increased breathing effort under additional oxygen for a pulse oximetry above 92%. Patients with cardiogenic pulmonary edema or exacerbation of chronic lung disease were excluded. All patients were treated with standard oxygen during the first period and with HFNC during the second. The primary outcome was the proportion of patients with improved respiratory failure 1 h after treatment initiation (respiratory rate $\leq$ 25 breaths/min without signs of increased breathing effort). Dyspnea and blood gases were also assessed.

Results: Among the 102 patients included, 48 were treated with standard oxygen and 54 with HFNC. One hour after treatment initiation, patients with HFNC were much more likely to recover from respiratory failure than those treated with standard oxygen: 61% (33 of 54 patients) versus 15% (7 of 48 patients), $P < 0.001$. They also showed greater improvement in oxygenation (increase in PaO_2 was 31 mm Hg [0–67] vs. 9 [−9–36], $P = 0.02$), and in feeling of breathlessness.

Conclusions: As compared to standard oxygen, patients with acute hypoxemic respiratory failure treated with HFNC at the ED had better oxygenation, less breathlessness and were more likely to show improved respiratory failure 1 h after initiation.

1. Introduction

During triage in emergency departments, dyspnea is one of the most common chief complaints, involving more than half of patients [1], and acute hypoxemic respiratory failure is a major cause of admission in ICU [2]. Usual first-line treatments include standard oxygen therapies through nasal cannula or non-rebreathing mask [3]. However, these devices have several limitations, especially for delivery of high and controlled inspired fractions of oxygen (FiO_2). Indeed, when delivered through standard oxygen devices, even with a non-rebreathing mask, FiO_2 does not exceed 70% and may be decreased during acute hypoxemic respiratory failure [4], because the high inspiratory flow generated by patients leads to dilution of inhaled oxygen with room air.

High-flow nasal cannula (HFNC) oxygen therapy is a technique of oxygenation first used in preterm infants [5,6] and more recently in intensive care units [7-12] or postoperative patients [13-15]. HFNC is able to deliver high and controlled FiO_2 up to 100%, even during acute respiratory distress [4]. Although without pressure support, the high flow generates a low level of positive pressure in the upper airway and subsequent positive end-expiratory pressure effect, which decreases with gas flow and open-mouth breathing [16,17]. Another physiological effect is continuous washout of dead space in the upper airways [18,19]. All these physiological effects may help to improve gas exchange and reduce respiratory rate and the work of breathing [17,20]. Pilot studies have shown better comfort and tolerance to therapy with acute respiratory fai-

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lure under HFNC than under standard oxygen therapy or noninvasive ventilation, probably due to the interface and the heated and humidified gas delivered by HFNC [7,11,21,22].

Benefits were reported in patients admitted in ICU for acute hypoxemic respiratory failure in terms of mortality [9], and emerging literature has described benefits of HFNC in an emergency setting including absolute variations of respiratory rate or comfort scales [21]. Moreover, previous studies conducted in EDs comparing HFNC and standard oxygen have included unselected patients admitted for acute respiratory failure due mainly to exacerbation of chronic lung disease or cardiogenic pulmonary edema [23-27]. Benefits of HFNC in selected patients admitted to the ED for acute hypoxemic respiratory failure have been only sparsely reported, particularly in early management [28,29].

The aim of the present before-after study was to compare the efficiency in respiratory failure regression of HFNC versus standard oxygen in patients admitted to the ED for acute hypoxemic respiratory failure.

2. Methods

2.1. Design and setting

We conducted an observational prospective before-after study between December 2015 and April 2017 in the EDs of two French centers including one teaching hospital, the University Hospital of Poitiers, and one general hospital, the General Hospital of Niort (NCT03447457). The independent ethics committee of the university hospital of Poitiers approved the study (2015–17). Accordingly, patients and/or their next of kin were informed and gave their consent before being included in the study.

2.2. Patients

All patients admitted to ED with acute hypoxemic respiratory failure were screened at their arrival in ED and could be enrolled if they fulfilled one of the following criteria: a respiratory rate of >25 breaths per minute, or signs of increased breathing effort including accessory respiratory-muscle activity or thoraco-abdominal asynchrony, despite additional standard oxygen for at least 15 min, in order to maintain pulse oximetry above 92%.

The main exclusion criteria were the following: a clinical diagnosis of cardiogenic pulmonary edema, acute exacerbation of chronic lung disease (based on clinical history, clinical presentation and blood gas analysis), long-term oxygen therapy or ventilatory support for chronic lung disease (such as chronic obstructive pulmonary disease GOLD 3, pulmonary fibrosis, obesity hypoventilation syndrome…), respiratory acidosis (pH < 7.35 and $PaCO_2$ > 50 mm Hg), hemodynamic instability (mean arterial pressure < 65 mm Hg, use of vasopressors), a Glasgow Coma Scale score of 12 points or less, an urgent need for endotracheal intubation, life expectancy of <3 months, a high degree of dependence defined by a World Health Organization Performance Status (WHOPS) score >3 [30]. Prior inclusion in the study was also an exclusion criterium.

2.3. Interventions

Patients were systematically treated with standard oxygen from November 2015 to May 2016 (before) and with HFNC from June 2016 to April 2017 (after). Between the two periods, a standardized education program involving all nurses and physicians at each ED was performed by investigators prior to HFNC implementation.

During the first period, standard oxygen was delivered through nasal cannula, face mask or non-rebreathing reservoir mask according to severity of patients and to the decision of the physician in charge. The flow rate was adjusted to maintain pulse oximetry at 92% minimum. During the second period, HFNC was continuously applied via large-bore nasal prongs with a gas flow rate set at 50 L/min and a FiO_2 adjusted to maintain pulse oximetry at 92% minimum with a dedicated device (Airvo™ 2, Fisher and Paykel Healthcare, Auckland, New-Zealand) equipped with a heated humidifier (MR850, Fisher and Paykel Healthcare, Auckland, New-Zealand). High-flow oxygen was applied 1 h minimum and switched to standard oxygen if signs of ARF had disappeared.

In each group, patients were monitored in the ED for at least 4 h. They were admitted to ICU if they had persistent or worsening signs of respiratory failure. Intubation criteria included a respiratory rate of >40 breaths per minute, signs of increased breathing effort, SpO_2 of <90% despite high FiO_2 or acidosis with a pH of <7.35, occurrence of hemodynamic instability or deterioration of neurologic status, as previously described [9].

2.4. Data collection

Clinical parameters, respiratory rate, pulse oximetry and signs of increased breathing effort were assessed at inclusion, 30 min and at 1 h (H1) after initiation of oxygenation strategies. Tolerance to the therapy was reported by the patient using a simplified visual analogic scale from 0 (maximal imaginable discomfort) to 10 (no discomfort) at inclusion, 30 min and H1 after initiation of oxygenation strategies [7,9]. The patient's feeling of dyspnea was assessed 30 min and H1 after initiation of each oxygenation strategy using a 5-point Likert scale (marked improvement, slight improvement, no change, slight deterioration or marked deterioration) [9,31]. Oxygenation was assessed with arterial blood gas at inclusion and 1 h after initiation of oxygenation strategy. We also assessed ergonomic and workload aspects by reporting nurses' experience of HFNC preparation or application and its subjective efficiency. The amount of workload included monitoring of clinical parameters, tolerance to and compliance with oxygen devices.

2.5. Study outcomes

The primary outcome was the proportion of patients presenting improved signs of respiratory failure 1 h after initiation of the two oxygen strategies. Improved signs of respiratory failure included reduction of the respiratory rate <25 breaths per minute and regression of signs of increased breathing effort including accessory respiratory-muscle activity and/or thoraco-abdominal asynchrony.

Secondary outcomes included comparisons of tolerance to the therapy, grade of dyspnea, blood oxygenation, ventilator support escalation, ICU admissions and day-28 mortality. We also assessed nurses' ease of use of HFNC and standard oxygen.

2.6. Statistical analysis

We planned to include 98 patients so as to show a significant decrease (25%) in the proportion of patients with signs of respiratory failure at 1 h after initiation of each oxygenation strategy, according to the results of our previous study showing the difference between patients with acute hypoxemic respiratory failure 1 h after initiation of HFNC and standard oxygen [7]. The number of patients was calculated by assuming that 15% of patients would have regression of respiratory failure at H1 with standard oxygen versus 40% with HFNC, with alpha risk of 5% and study power of 80%.

Quantitative variables were expressed as median and (25th–75th) percentiles, and qualitative variables were expressed as number and percentage. Qualitative data were compared using the chi-square test or Fisher test when appropriate. Quantitative data were compared using Student's *t*-test or the Mann-Whitney *U* test for continuous variables. Variables associated with regression of respiratory failure were assessed by means of multivariate logistic-regression analyses using a backward-selection procedure. Variables suspected to be linked with acute respiratory failure regression with a $P < 0.20$ after univariate analysis were entered into the maximal model. A two-tailed P-value of <0.05 was considered as statistically significant. Statistical analysis was performed using SPSS 23.0 software (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patients

A total of 102 patients with acute hypoxemic respiratory failure were included, after secondary exclusion of 4 with acute or chronic lung disease, 2 with cardiogenic pulmonary edema, and 1 with a high degree of dependence. Among them, 48 patients were treated with standard oxygen from November 2015 to May 2016 (first period), and 54 were treated with HFNC from June 2016 to April 2017 (second period) after a washout and educational period of one month.

The characteristics of the patients at enrollment were similar in both groups, except for oxygen flow rate (Table 1). The main cause of acute respiratory failure was community-acquired pneumonia in 81 patients (79%), with a bilateral pulmonary infiltrate in 70 patients (69%). At inclusion, 83 patients (81%) exhibited signs of increased breathing effort while the median respiratory rate was 32 breaths per min (interquartile range (IQR), 28–36) and PaO_2 was 63 mm Hg (IQR 55–75).

3.2. Primary outcome

As compared to standard oxygen, patients treated with HFNC were much more likely to show improved signs of respiratory failure at H1: 61% (33 out of 54 patients) vs. 15% (7 out of 48 patients), $P < 0.001$. The analysis of variance showed a significant difference at baseline, 30 min and H1 (Table 2, Figs. 1 and 2).

3.3. Secondary outcomes

Although comfort was similar, a higher proportion of patients felt improvement of their dyspnea under HFNC than under standard oxygen at H1 (Table 2): 92% (44 of 48 patients) versus 56% (20 out of 36 patients), $P < 0.01$.

Patients treated with HFNC showed greater improvement of oxygenation than those treated with standard oxygen with an increase in PaO_2 of 31 mm Hg (IQR 0–67) vs. 9 (IQR −9–36) 1 h after treatment initiation ($P = 0.02$) (Table 2). $PaCO_2$ did not change significantly between baseline and 1 h after treatment initiation: for patients treated with standard oxygen, $PaCO_2$ was 37 mm Hg (IQR 32–41) at baseline versus 36 (IQR 33–42) at H1 ($P = 0.64$), and with HFNC 36 mm Hg (IQR 31–39) at baseline versus 34 (IQR 31–39) ($P = 0.54$).

NIV was applied in 6% of the cases (6 out of 102 patients), without any significant difference between the two oxygen strategies, and no patient required urgent intubation before ICU admission (Table 2). Length of stay in an ED did not differ between groups and even tended to be shorter in patients treated with HFNC than in those treated with standard oxygen, 5 h (IQR, 3–9) versus 8 (IQR, 4–12) ($P = 0.08$).

The proportion of patients requiring admission to ICU did not differ between groups: 54% (29 out of 54 patients) in the HFNC group versus 42% (20 out of 48 patients) in the standard oxygen group ($P = 0.24$). The only reasons for ICU admission were persistent, worsening respiratory failure or need for intubation. Intubation rates during the ICU stay did not differ between groups: 31% (9 of 29 patients) were intubated in HFNC group and 40% in standard oxygen group (8 of 20 patients) ($P = 0.73$). Mortality at day 28 was similar between groups (Table 2).

Among the 33 nurses interviewed, 14 (42%) found that HFNC was easier to use than standard oxygen, while it was similar for 12 nurses (36%), and less easy to use for 7 nurses (21%). For 13 nurses (39%) HFNC entailed less workload whereas it was similar for 13 other nurses (39%) and entailed more workload for the other 6 nurses (18%). Among them, 27 nurses (82%) were more confident with the use of HFNC than with standard oxygen and 28 nurses (85%) estimated that patients were more comfortable under HFNC.

Table 1
Comparison of patient characteristics at baseline during the two periods of oxygen strategies.[a]

Characteristics	Standard oxygen ($n = 48$)	High-flow oxygen ($n = 54$)	P value
Age, y, median (IQR)	68 [59–85]	73 [61–84]	0.44
Body mass index kg/m^2, median (IQR)	25 [22–29]	27 [23–31]	0.38
Reason for de novo respiratory failure, no. (%)			0.30
Pneumonia	35 (73)	46 (85)	
Asthma	2 (4)	1 (2)	
Other	11 (23)	7 (13)	
Comorbidities, no. (%)			
History of cardiac insufficiency	17 (35)	10 (18)	0.06
Immunodeficiency	6 (12)	15 (28)	0.05
Smoker	10 (21)	7 (13)	0.31
Mild chronic obstructive pulmonary disease	2 (4)	10 (18)	0.02
Liver cirrhosis	2 (4)	1 (2)	0.34
Clinical parameters at baseline			
Respiratory rate, breaths/min, median (IQR)	32 [28–40]	32 [28–36]	0.62
Signs of increased WOB[b], no. (%)	36 (75)	47 (87)	0.12
Bilateral pulmonary infiltrate, no (%)	32 (67)	38 (70)	0.93
Oxygen flow, liters/min, median (IQR)[c]	4 [3–6]	6 [3–9]	0.04
Arterial blood gas			
pH, units, median (IQR)	7.45 [7.31–7.48]	7.43 [7.29–7.47]	0.48
$PaCO_2$, mm Hg, median (IQR)	37 [32–41]	36 [31–39]	0.15
PaO_2, mm Hg, median (IQR)	63 [58–78]	62 [52–73.8]	0.15
PaO_2/FiO_2[d]	200 [154–246]	166 [128–212]	0.02
Other therapeutics			
Antibiotics	38 (79)	43 (80)	0.95
Bêta2 agonist	7 (15)	6 (11)	0.60
Steroids	13 (27)	16 (33)	0.62
Diuretics	16 (33)	13 (24)	0.44

Abbreviations: IQR, interquartile range; WOB, work of breathing.
[a] Data are presented as no. (%), median (IQR).
[b] Signs of increased WOB included accessory respiratory-muscle activity and thoraco-abdominal asynchrony.
[c] All patients were treated with standard oxygen therapy at baseline.
[d] FiO_2 was calculated according the following formula – $0.21 + 0.03 \times$ oxygen flow.

3.4. Factors associated with regression of respiratory failure

All in all, 39% of patients (40 out of 102) exhibited regression of respiratory failure 1 h after initiation of oxygen strategies (Table 3). Patients with regression of respiratory failure had a lower respiratory rate and less frequently showed signs of increased breathing effort at baseline and were more likely to have been treated with HFNC. After multivariate logistic regression analysis, regression of respiratory failure remained independently associated with HFNC and respiratory rate at baseline (Table 4).

4. Discussion

In this prospective before-after study conducted at the ED, we found that early management with HFNC of patients admitted for acute hypoxemic respiratory failure resulted in improved signs of respiratory failure in a significant higher proportion as compared to standard oxygen. In addition, patients' feeling of dyspnea

Table 2
Evolution of respiratory parameters and outcomes during the two periods of oxygen strategies.[a]

Respiratory parameters and outcomes	Standard oxygen (*n* = 48)	High-flow oxygen (*n* = 54)	*P* value
Oxygen variables at H1, median (IQR)			
Flow, L/min	6 [3–10]	50 [50–50]	<0.001
FiO_2, %[e]	39 [30–50]	72 [50–95]	<0.001
Respiratory rate < 25 breaths/min, no. (%)			
30 min	11 (21)	26 (46)	0.005
H1	15 (31)	35 (65)	0.001
Improvement in signs of increased WOB[b], no. (%)			
30 min	15 (31)	35 (65)	<0.001
H1	19 (40)	44 (81)	<0.001
Regression of respiratory failure, no. (%)			
30 min	5 (10)	16 (30)	0.017
H1	7 (15)	33 (61)	<0.001
Respiratory patient – comfort[c] (IQR), points			
30 min	8 [5–10]	8 [7–9]	0.80
H1	8 [5–10]	8 [7–9]	0.30
Grade of dyspnea at H1, no. of patients/total no. (%)			0.001
Marked improvement	4/36 (11)	21/48 (44)	
Slight improvement	16/36 (45)	23/48 (48)	
No change	12/36 (33)	3/48 (6)	
Slight deterioration	3/36 (8)	1/48 (2)	
Marked deterioration	1/36 (3)	0 (0)	
Arterial blood gas parameters at H1, median (IQR)			
pH, units	7.44 [7.39–7.47]	7.44 [7.41–7.47]	0.82
$PaCO_2$, mm Hg	36 [33–42]	34 [31–39]	0.09
PaO_2, mm Hg,	75 [67–107]	93 [66–130]	0.13
Change in PaO_2[d], mm Hg	9 [−9–36]	31 [0–67]	0.02
ED length of stay, h, median (IQR)	8 [4–12]	5 [3–9]	0.08
ICU admission, no. (%)	20 (42)	29 (54)	0.24
Respiratory failure	20 (100)	29 (100)	1
Hemodynamic failure	0 (0)	1 (3)	1
Neurological failure	0 (0)	0 (0)	1
NIV initiation, no. (%)	3 (6)	3 (6)	1
Intubation rate, no (%)	8 (17)	9 (17)	1
Mortality at day 28, no. (%)	7 (15)	6 (11)	0.77

Abbreviations: IQR, interquartile range; WOB, work of breathing.
[a] Data are presented as no. (%), median (IQR). Difference is reported as median difference (IQR).
[b] Signs of increased WOB included signs of high respiratory-muscle workload, thoraco-abdominal asynchrony.
[c] Comfort under oxygen therapy devices were evaluated with a simplified visual analogic scale ranging 0 to 10.
[d] Increase in PaO_2 is the difference between PaO_2 1 h after initiation and baseline of oxygen strategy.
[e] FiO_2 was calculated according the following formula – $0.21 + 0.03 \times$ oxygen flow.

was significantly improved under HFNC, with more pronounced oxygenation improvement. However, there was no difference in terms of ICU admissions, intubation or mortality rates.

4.1. Effect of HFNC on acute respiratory failure

The HFNC system contributes to improved blood oxygenation through several physiological effects [32], including control of the FiO_2 inhaled during inspiration. The high flow delivered by the system exceeds the high peak inspiratory flow generated by patients during acute hypoxemic respiratory failure and thereby mitigates the dilution of inspired oxygen with room air [4]. Another effect of the system is to generate a low level of positive pressure in the upper airway directly proportional to the gas flow delivered, thereby possibly improving oxygenation [16,17]. Indeed, improvement of oxygenation under HFNC was first reported in pilot studies including ICU patients with acute respiratory failure [7,11,12,33]. In our study, changes of oxygenation were effectively higher under HNFC as compared to standard oxygen within the first hour of initiation, reflecting a good matching between patient inspiratory flow and FiO_2 delivered by HFNC.

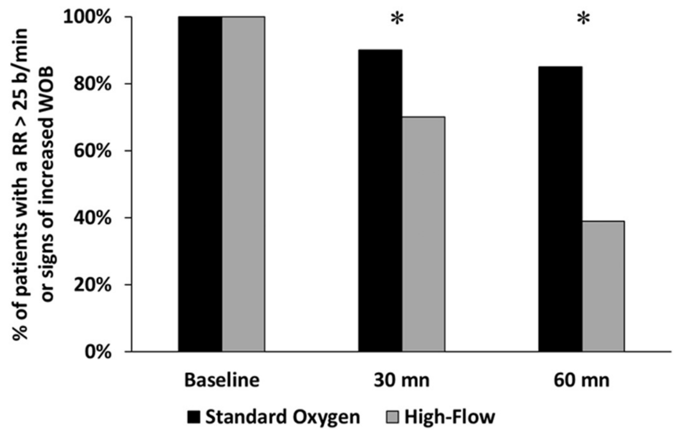

Fig. 1. Comparison of patients with respiratory distress defined by signs of increased breathing effort or respiratory rate (RR) > 25 breaths/min at baseline, 30 min and 60 min after initiation of standard oxygen (black bars) and high-flow nasal cannula oxygen (grey bars).*$P < 0.05$.

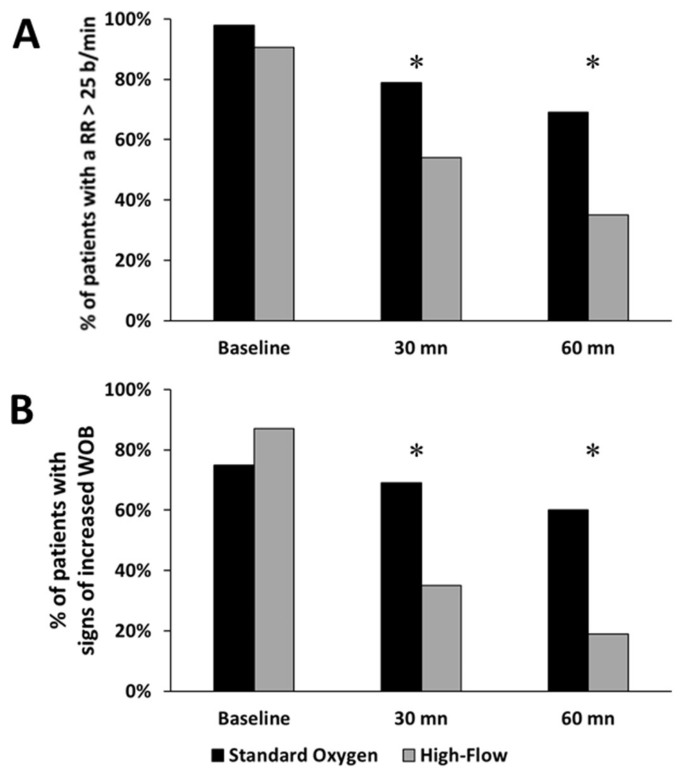

Fig. 2. A, Comparison of patients having a respiratory rate (RR) > 25 breaths/min at baseline, 30 min and 60 min after initiation of oxygen strategies; B, comparison of patients showing signs of increased breathing effort at baseline, 30 min and 60 min after initiation of standard oxygen (black bars) and high-flow nasal cannula oxygen (grey bars).*$P < 0.01$.

HFNC may also provide ventilatory support favoring reduction of the work of breathing and respiratory rate [16,20,34]. Delorme et al. reported in a physiological study including patients recovering from acute hypoxemic respiratory failure that HFNC leads to

Table 3
Comparison between patients with regression of respiratory distress and with persistence of respiratory distress under oxygen strategies.[a]

	Regression of respiratory failure (n = 40)	Persistence of respiratory failure (n = 62)	P value
Age (IQR), y	71 [61–83]	70.2 [60–86]	0.58
Sex, male, no. (%)	27/40 (67)	35/62 (56)	0.26
Reason for de novo respiratory failure, no. (%)			
Pneumonia	35 (87.5)	54 (87.1)	0.95
Other	5 (12.5)	8 (12.9)	0.95
Comorbidities, no. (%)			
History of cardiac insufficiency	10 (25)	17 (27)	0.79
Immunosuppression	11 (18)	10 (25)	0.38
Tobacco	8 (20)	9 (15)	0.47
Clinical parameters at baseline			
Respiratory rate, breaths/min	30 [27–34]	34 [30–40]	<0.01
Signs of increased WOB[b], no. (%)	30 (75)	53 (85)	0.18
Bilateral pulmonary infiltrate, no (%)	28 (70)	42 (68)	0.81
Arterial blood gas at baseline, median (IQR)			
pH, units	7.44 [7.40–7.48]	7.43 [7.40–7.47]	0.85
$PaCO_2$, mm Hg	36 [31–41]	36 [32–41]	0.85
PaO_2, mm Hg	63 [53–74]	63 [55–78]	0.73
Oxygen strategies, no. (%)			<0.01
High-flow oxygen	33 (82)	21 (34)	
Standard oxygen	7 (17)	41 (66)	
Other therapeutics			
Antibiotics	29 (72)	52 (84)	0.17
Bêta2 agonist	9 (22)	20 (32)	0.29
Steroids	4 (10)	9 (14)	0.50
Diuretics	12 (30)	17 (27)	0.78

Abbreviations: IQR, interquartile range; WOB, work of breathing.
[a] Data are presented as No. (%), median (IQR).
[b] Signs of increased WOB included signs of high respiratory-muscle workload, thoraco-abdominal asynchrony.

Table 4
Factors associated with regression of respiratory distress, defined by a respiratory rate <25 breaths per minute and improvement of signs of increased breathing effort

	Odds ratio	IC (95%)	P value
Respiratory rate at baseline, breaths/min	0.90	0.83–0.98	0.01
Treatment by HFNC	15.45	4.69–50.88	<0.001

Respiratory rate at baseline, presence of signs of increased work of breathing at baseline and oxygen strategies were entered into the maximal model.

significant reduction in all indexes of respiratory effort (assessed by the measurement of esophageal pressure) proportionally to the flow rate delivered through the device (increasing from 20, 40 to 60 L/min) [34]. The high-flow rate of gas continuously delivered in the upper airways may generate a washout of dead space and then flush out carbon dioxide, thereby decreasing patients' ventilatory demand [18,19]. In the present study, the respiratory rate decreased and signs of increased breathing effort improved rapidly under HFNC. Contrary to the previous studies, we aimed at showing a regression of signs of respiratory failure, meaning that patients had recovered, and our results indeed showed more than a regression of respiratory rate values. Makdee et al. showed a similarly rapid effect within 15 min after HFNC initiation in selected patients treated for cardiogenic pulmonary edema in ED, resulting in a greater decrease of respiratory rate than after standard oxygen [25]. In unselected patients admitted to an ED for acute respiratory failure, Rittayamai et al. reported similar immediate effects of HFNC within 5 min as compared to standard oxygen, with a significant decrease in dyspnea score, despite a lower gas flow set (35 L/min) than the one used in our study (50 L/min) [26]. Bell et al. compared proportions of patients with acute respiratory failure exhibiting a reduced respiratory rate and feeling of dyspnea with standard oxygen and HNFC. They reported a higher proportion of patients with decreased respiratory rate under HNFC (67%) than under standard oxygen (38%) [23]. Moreover, the proportion of patients who felt improved dyspnea was markedly higher under HFNC (75%) than with standard oxygen (56%) [23]. In our study, the benefits of HFNC on regression of respiratory failure were surprisingly higher than those reported in previous studies, possibly due to the higher preset gas flow (50 L/min) applied in the HFNC system as compared to previous studies (35 to 50 L/min) [23,24,26]. Comfort under oxygenation strategies was similar between standard oxygen and HFNC, as no patient reported intolerance of devices leading to suspension of treatment. In previous studies, HFNC was generally better tolerated than standard oxygen despite high flow set up to 50 L/min [9-11]. This can be explained by the characteristics of the HFNC system, which delivers heated and humidified inhaled gas with a less restrictive interface [11,32].

4.2. Impact of HFNC on outcomes

Despite the benefits of HNFC as compared to standard oxygen on signs of respiratory failure, we did not find any difference in outcomes in terms of ICU admissions, intubation rate or mortality. This contrasts with the findings of the study reported by Frat et al. comparing HFNC, standard oxygen and NIV in ICU patients with acute hypoxemic respiratory failure. This study was in disfavor of standard oxygen or NIV as compared to HFNC in terms of mortality and intubation rates. The discrepancy with our results can be explained by the lower severity of patients included in our study and their early management of acute hypoxemic respiratory failure on ED admission. Otherwise, very few studies have compared intubation rates during hospital stay after early application of standard oxygen or HNFC in an ED. Results showed very low intubation rates (<1%) [23,24], probably due to second-line treatment with NIV applied in a population of unselected patients presenting mainly with COPD exacerbation or cardiogenic pulmonary edema. Indeed, NIV has repeatedly shown benefits in these indications [23,24,35,36]. Finally, HFNC was used for days in ICU, explaining the substantial benefits observed in prior studies [9].

The length of stay of patients in the ED did not differ between the two groups in our study, despite a trend toward lower stay in patients treated with HFNC. This suggests the absence of impact of HNFC on care monitoring or nurse organization and the beneficial impact of the educational program applied during the study.

4.3. Clinical implications

These results encourage use of HFNC as an alternative to standard oxygen devices in EDs in management of patients with acute hypoxemic respiratory failure. However, future studies are needed to confirm the benefits of HFNC in terms of outcomes when applied early in ED. One limitation of our study is due to its before-after design. A before-after study was chosen mainly due to ethical considerations. According to the results of previous physiological and clinical studies conducted in ICU reporting benefits of HFNC and in order to preserve equipoise, we preferred to compare a period when HFNC was not available in an ED with another period when availability expanded its possible use to all patients. Second, the first inclusion period was shorter (standard oxygen period) than the second (HFNC period). This can be explained by a higher rate of pneumonia as reason for ED admission in winter (standard oxygen period) than in summer (HFNC period). Indeed, the patients included in the study were largely selected with mainly community-acquired pneumonia, a factor leading us to consider our results applicable to this type of homogeneous population. On the other hand, use of HFNC in an ED involves severe patients, who must be closely monitored, applying prespecified criteria for ICU admission or intubation. Third, there was an imbalance between groups as concerned immunocompromised patients. This should not have skewed results, as a recent large randomized trial did not report any difference in intubation rates and mortality between HFNC and standard oxygen in this population [37]. Similarly, there were more patients with mild chronic obstructive disease in the HFNC group, but no prospective study has been conducted in this setting. Under these conditions, implementation of HFNC at the ED does not seem to increase nurse workload in terms of monitoring and length of stay at the ED, and it also appears to be efficient in improving signs of respiratory failure.

5. Conclusions

Treatment with HFNC produced rapid alleviation of signs of respiratory failure in subjects with acute hypoxemic respiratory failure admitted to an ED. HFNC was well-tolerated, as easy to use as standard oxygen therapy without increase in nurses' workloads. These results suggest that HFNC may be considered as an alternative to standard oxygen for eligible patients with acute hypoxemic respiratory failure admitted to an ED. To establish the clinical impact of early application of HFNC in this setting, a well-designed prospective randomized trial is required.

Conflicts of interest

JPF reports grants, personal fees and non-financial support from the "Fisher & Paykel Health Care" firm, during the conduct of the study; personal fees and non-financial support from SOS oxygène, exterior to the submitted work.

RC reports non-financial support from MSD, exterior to the submitted work.

JM, FF, OM, MF, MV, P-A B, JG, SR and A-W T: none declared.

The firm Fisher and Paykel Health Care provided equipment to the participating centers, but had no other implication in the study.

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