Predictors of Intubation in Patients With Acute Hypoxemic Respiratory Failure Treated With a Noninvasive Oxygenation Strategy*

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Objectives: In patients with acute hypoxemic respiratory failure, noninvasive ventilation and high-flow nasal cannula oxygen are alternative strategies to conventional oxygen therapy. Endotracheal intubation is frequently needed in these patients with a risk of delay, and early predictors of failure may help clinicians to decide early. We aimed to identify factors associated with intubation in patients with acute hypoxemic respiratory failure treated with different noninvasive oxygenation techniques.

Design: Post hoc analysis of a randomized clinical trial.

Setting: Twenty-three ICUs.

Patients: Patients with a respiratory rate greater than 25 breaths/min and a Pao_2/Fio_2 ratio less than or equal to 300 mm Hg.

Intervention: Patients were treated with standard oxygen, high-flow nasal cannula oxygen, or noninvasive ventilation.

Measurement and Main Results: Respiratory variables one hour after treatment initiation. Under standard oxygen, patients with a respiratory rate greater than or equal to 30 breaths/min were more likely to need intubation (odds ratio, 2.76; 95% CI, 1.13–6.75; $p = 0.03$). One hour after high-flow nasal cannula oxygen initiation, increased heart rate was the only factor associated with intubation. One hour after noninvasive ventilation initiation, a Pao_2/Fio_2 ratio less than or equal to 200 mm Hg and a tidal volume greater than 9 mL/kg of predicted body weight were independent predictors of intubation (adjusted odds ratio, 4.26; 95% CI, 1.62–11.16; $p = 0.003$ and adjusted odds ratio, 3.14; 95% CI, 1.22–8.06; $p = 0.02$, respectively). A tidal volume above 9 mL/kg during noninvasive ventilation remained independently associated with 90-day mortality.

Conclusions: In patients with acute hypoxemic respiratory failure breathing spontaneously, the respiratory rate was a predictor of intubation under standard oxygen, but not under high-flow nasal cannula oxygen or noninvasive ventilation. A Pao_2/Fio_2 below 200 mm Hg and a high tidal volume greater than 9 mL/kg were the two strong predictors of intubation under noninvasive ventilation. (*Crit Care Med* 2018; 46:208–215)

Key Words: acute respiratory failure; high-flow nasal cannula; high-flow oxygen therapy; intubation; noninvasive ventilation

Patients admitted to the ICU for acute hypoxemic respiratory failure may receive different forms of noninvasive oxygenation techniques including face mask oxygen, noninvasive ventilation (NIV) (1, 2) and high-flow nasal cannula (HFNC) (3), with the aim of avoiding endotracheal intubation. The use of NIV in these patients is debated because intubation rates remain high (around 40–50%) and mortality rates reach 50% when NIV fails (4–9). NIV and HFNC have been suggested to potentially delay intubation by masking signs of respiratory distress (6, 10, 11).

A multicenter randomized controlled trial comparing different strategies of oxygenation recently found that patients with acute hypoxemic respiratory failure treated by HFNC had a lower mortality rate than those treated by HFNC associated with NIV, a finding possibly explained by a lower intubation rate in severe hypoxemic patients treated by HFNC (8). This result could lead to consideration of HFNC as a potential first-line strategy for the management of acute hypoxemic respiratory failure and also raises the question of the safety of NIV in the same group. In the recent large international Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study, severe hypoxemic patients who failed NIV had a higher mortality rate (approximately 43%) than those invasively ventilated (9).

With these data in mind, identification of factors associated with intubation under these techniques may help the clinician to avoid an unnecessary and potentially harmful prolongation of a noninvasive strategy of oxygenation (6, 11). Indeed, the factors predicting intubation after NIV failure have been identified only from cohort studies or surveys (4, 6, 7, 11). They include disease severity and variables that are considered, per se, as intubation criteria and are consequently poor predictors for an early decision to intubate. On the other hand, few studies to date have assessed risk factors of intubation in patients treated with HFNC.

Therefore, in a post hoc analysis of a large-scale randomized controlled trial, we aimed to identify early factors associated with intubation and 90-day mortality in patients admitted to the ICU for acute hypoxemic respiratory failure and treated with a noninvasive strategy of oxygenation, including standard oxygen, HFNC, and NIV.

Some of the results of this post hoc analysis have been reported under abstract form at the 2017 meeting of the French Intensive Care Society in Paris, France (12).

MATERIAL AND METHODS

Study Population and Design

We performed a post hoc analysis of a randomized controlled trial conducted in 23 centers in France and Belgium (8). In this study, 310 patients admitted to ICU with acute respiratory failure were randomly assigned to receive a treatment by standard oxygen, HFNC, or NIV. All patients had a respiratory rate of more than 25 breaths/min, a Pao_2/Fio_2 ratio below or equal to 300 mm Hg, and a $Paco_2$ not higher than 45 mm Hg. The main exclusion criteria were severe neutropenia, acute-on-chronic respiratory failure, cardiogenic pulmonary edema, shock, or altered consciousness.

The original trial was approved by ethics committees at Centre Hospitalier Universitaire de Poitiers for French study sites and at Cliniques Universitaires Saint-Luc, Brussels, for the site in Belgium. Written informed consent was obtained from all the patients, their next of kin, or another surrogate decision maker as appropriate. According to the French law, this secondary analysis of the original study did not need ethics approval.

Oxygen Strategies

Standard oxygen was applied continuously through a nonrebreathing mask at a flow rate of at least 10 L/min. HFNC was applied continuously via large-bore binasal prongs at a gas flow of 50 L/min (Optiflow; Fisher & Paykel Healthcare, Auckland, New Zealand). NIV was delivered through a face mask at least

8 hours minimum per day interspaced with HFNC between NIV sessions. Pressure-support level was adjusted to obtain a tidal volume between 7 and 10 mL/kg of predicted body weight (PBW), whereas positive end-expiratory pressure (PEEP) was adjusted around 5 cm H_2O and then readjusted according to hypoxemia. Whatever the strategy chosen, gas flow, F_{IO_2}, and/or PEEP level were set to maintain pulse oximetry (Sp_{O_2}) greater than or equal to 92%.

Data Collection and Predetermined Criteria for Intubation

Clinical variables, ventilatory variables, and blood gas samples were collected at baseline during spontaneous breathing with a nonrebreathing mask and 1 hour after initiation (H1) of the allocated treatment by the randomization (standard oxygen, HFNC, or NIV).

Criteria for endotracheal intubation were predetermined and consisted in 1) signs of persisting or worsening respiratory failure including at least two of the following criteria: respiratory rate above 40 breaths/min, lack of improvement of signs of high respiratory muscle workload, development of copious tracheal secretions, pH below 7.35, or Sp_{O_2} below 90% for more than 5 minutes; 2) hemodynamic instability; or 3) deterioration of neurologic status (8).

Study Outcomes

Our main outcome was to identify early factors associated with intubation, that is, at baseline and 1 hour after initiation of each treatment. The second outcome was to identify factors associated with mortality at day 90.

Statistical Analysis

Continuous variables were expressed as mean ± SD or median (25–75th percentiles) when appropriate. Qualitative variables were expressed as frequency and percentage.

Intubated and not intubated patients were compared using the chi-square for categorical variables and the Student's *t* test or the Mann-Whitney *U* test for continuous variables. Categorization of quantitative data was performed using a receiver operating characteristic curve and Youden's index.

Variables associated with intubation were assessed by means of multivariate logistic regression analyses, and results are given as odds ratio (OR) with their 95% CIs. Variables associated with mortality at 90 days were assessed by means of Cox proportional hazard regression analysis, and results are given as hazard ratio with 95% CI. A backward manual selection procedure was performed for the maximal model using all factors associated with outcomes with a p value of less than 0.10. All interactions were tested. The final model included variables significantly associated with intubation and mortality.

Concordance (c) index was calculated to indicate discrimination ability of models: area under the curve for the logistic regression and concordance for survival time data (SAS macro by Kremers, Walter, September 18, 2008).

A two-tailed p value of less than 0.05 was considered as statistically significant. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Characteristics of Patients and Treatments

Of the 310 patients included in the study, 72 patients (23%) had mild hypoxemia (Pa_{O_2}/F_{IO_2} ratio between 201 and 300 mm Hg), 165 patients (53%) had moderate hypoxemia (Pa_{O_2}/F_{IO_2} ratio between 101 and 200 mm Hg), and 73 patients (24%) had severe hypoxemia (Pa_{O_2}/F_{IO_2} ratio ≤ 100 mm Hg) (**Table 1**; and **e-Table 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/C967).

Among the 310 patients, 94 patients were treated with standard oxygen, 106 with HFNC, and 110 with NIV. The mean gas flow was 13 ± 5 L/min in patients treated with standard oxygen and 48 ± 11 L/min in those treated with HFNC, with a F_{IO_2} 0.82 ± 0.20. In patients treated with NIV, levels of pressure support and PEEP were 8 ± 3 and 5 ± 1 cm H_2O, respectively, with F_{IO_2} 0.67 ± 0.24, resulting in a mean expired tidal volume of 560 ± 180 mL 1 hour after NIV initiation. The median of expired tidal volume was 8.7 mL/kg (7.3–10.4 mL/kg) of PBW. The duration of NIV was 8 hours (4–12 hr) at day 1 and 8 hours (4–13 hr) at day 2.

In the overall population, 45% (139/310 patients) needed intubation. The main reason for intubation consisted in signs of persisting or worsening respiratory failure in 92% of the cases (128 of the 139 intubated patients). Patients who needed intubation had higher respiratory rate and lower Pa_{O_2} at baseline than the others and were more likely to have bilateral pulmonary infiltrates (Table 1).

Factors Associated With Intubation in Patients Treated With Standard Oxygen

In patients treated with standard oxygen, 47% (44/94 patients) needed intubation. Patients who needed intubation had higher respiratory rate and were more likely to have bilateral pulmonary infiltrates than the others (**Table 2**; and **e-Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCM/C967). After multivariate logistic regression analysis, the only factor independently associated with intubation was a respiratory rate greater than or equal to 30 breaths/min under standard oxygen 1 hour after initiation: OR, 2.76 (95% CI, 1.13–6.75; $p = 0.03$) (**Table 3**).

Factors Associated With Intubation in Patients Treated With HFNC

In patients treated with HFNC, 38% (40/106 patients) needed intubation. One hour after initiation of HFNC, no respiratory variable was associated with intubation (Table 2; and **e-Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCM/C967). After multivariate logistic regression analysis, the only factor independently associated with intubation was increased heart rate 1 hour after initiation: OR, 1.03 (95% CI, 1.01–1.06; $p < 0.01$) (Table 3).

Factors Associated With Intubation in Patients Treated With NIV

In patients treated with NIV, 50% (55/110 patients) needed intubation. Although pressure support and PEEP levels were similar between the patients who were intubated and the others,

TABLE 1. Comparison of Baseline Characteristics of Patients Who Required or Not Intubation

Demographic and Clinical Data	Not Intubated ($n = 171$)	Intubated ($n = 139$)	p
Characteristics of the patients			
Age (yr), mean ± SD	60 ± 17	62 ± 17	0.17
Male sex, *n* (%)	112 (65)	100 (72)	0.22
Body mass index, kg/m^2, mean ± SD	26 ± 5	26 ± 6	0.88
Simplified Acute Physiologic Score II at inclusion, points, mean ± SD	25 ± 9	26 ± 9	0.11
Immunosuppression, *n* (%)	44 (26)	38 (27)	0.75
Bilateral pulmonary infiltrates, *n* (%)	125 (73)	119 (86)	0.007
Community-acquired pneumonia, *n* (%)	112 (65)	85 (61)	0.43
Clinical variables at baseline, mean ± SD			
Respiratory rate, breaths/min	32 ± 6	33 ± 7	0.03
Heart rate, beats/min	104 ± 19	108 ± 19	0.05
Systolic arterial pressure, mm Hg	128 ± 24	128 ± 20	0.98
Arterial blood gas at baseline, mean ± SD			
pH, units	7.43 ± 0.06	7.44 ± 0.06	0.24
$Paco_2$, mm Hg	35 ± 6	35 ± 6	0.56
Pao_2, mm Hg	93 ± 35	83 ± 30	0.009
Pao_2/Fio_2 ratio, mm Hg	162 ± 83	147 ± 73	0.12
Degree of severity of hypoxemia at baseline, *n* (%) (mm Hg)			0.08
Pao_2/Fio_2 201–300	48 (28)	24 (17)	
Pao_2/Fio_2 101–200	86 (50)	79 (57)	
$Pao_2/Fio_2 \leq 100$	37 (22)	36 (26)	
Oxygenation strategies, *n* (%)			0.18
Noninvasive ventilation	55 (50)	55 (50)	
High-flow nasal cannula oxygen therapy	66 (62)	40 (38)	
Standard O_2 therapy	50 (47)	44 (53)	

the expired tidal volume 1 hour after NIV initiation was higher and more frequently exceeded 9 mL/kg of PBW in patients who needed intubation (**Fig. 1**; Table 2; and **e-Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/C967). After multivariate logistic regression analysis, the two factors independently associated with intubation were a Pao_2/Fio_2 ratio 1 hour after NIV initiation less than 200 mm Hg and an expired tidal volume exceeding 9 mL/kg of PBW 1 hour after NIV initiation: adjusted OR (aOR), 4.26 (95% CI, 1.62–11.16; $p = 0.003$) and aOR 3.14 (95% CI, 1.22–8.06, $p = 0.02$), respectively (Table 3).

Factors Associated With 90-Day Mortality

Mortality rates at day 90 were 27% (66/310 patients) in the overall population and 47% (66/139 patients) in patients who needed intubation (**e-Table 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/C967).

The interval between inclusion and intubation did not differ between patients who survived and those who died among groups: 16 hours (9–23 hr) versus 16 hours (15–28 hr) in NIV group ($p = 0.40$) (**Fig. 2**), 22 hours (12–29 hr) versus 21 hours (17–25 hr) in HFNC group ($p = 0.99$) and 17 hours (12–29) versus 18 hours (9–26 hr) in standard oxygen group ($p = 0.60$), respectively.

Patients who died were older, were more severe as indicated by higher Simplified Acute Physiology Score (SAPS) II, were more frequently immunocompromised, and were more frequently treated with standard oxygen or NIV (e-Table 5, Supplemental Digital Content 1, http://links.lww.com/CCM/C967). After Cox proportional hazard regression analysis, SAPS II was the only factor associated with mortality in patients treated with HFNC or standard oxygen. In patients treated with NIV, a tidal volume above 9 mL/kg of PBW 1 hour

TABLE 2. Comparison of Ventilatory Variables 1 Hour After Initiation of Standard Oxygen, Noninvasive Ventilation, or High-Flow Nasal Cannula Oxygen Therapy in Patients Who Required or Not Intubation

Ventilatory Data at 1 Hr	Not Intubated	Intubated	*p*
Patients treated by standard O_2 therapy	*n* = 50	*n* = 44	
Respiratory rate, breaths/min, mean ± SD	30 ± 7	33 ± 7	0.007
Respiratory rate ≥ 30 breaths/min[a], *n*, *n* total	22/50	29/41	0.01
Respiratory patient discomfort[b], mm, mean ± SD	34 ± 27	46 ± 29	0.06
Gas flow, L/min, mean ± SD	13 ± 3	15 ± 7	0.08
F_{IO_2}, %, mean ± SD	59 ± 20	57 ± 24	0.56
Pa_{O_2}/F_{IO_2} ratio, mm Hg, mean ± SD	157 ± 70	133 ± 67	0.14
Patient treated by high-flow nasal cannula oxygen therapy	*n* = 66	*n* = 40	
Respiratory rate, breaths/min, mean ± SD	27 ± 8	29 ± 5	0.18
Respiratory rate ≥ 30 breaths/min[a], *n*, *n* total	23/65	18/39	0.28
Respiratory patient discomfort[b], mm, mean ± SD	25 ± 23	36 ± 29	0.05
Gas flow, L/min, mean ± SD	47 ± 11	48 ± 18	0.87
F_{IO_2}, %, mean ± SD	82 ± 20	82 ± 21	0.99
Pa_{O_2}/F_{IO_2} ratio, mm Hg, mean ± SD	143 ± 78	119 ± 62	0.12
Patients treated by noninvasive ventilation	*n* = 55	*n* = 55	
Respiratory rate, breaths/min, mean ± SD	29 ± 8	32 ± 8	0.09
Respiratory rate ≥ 30 breaths/min, *n*, *n* total	21/53	34/54	0.015
Respiratory patient discomfort[b], mm, mean ± SD	40 ± 26	46 ± 32	0.27
Pressure-support[a], cm H_2O, mean ± SD	8.2 ± 2.9	8.7 ± 2.6	0.36
Positive end-expiratory pressure[a], cm H_2O, mean ± SD	5.1 ± 1.9	4.9 ± 1.1	0.70
F_{IO_2}[a], %, mean ± SD	63 ± 23	71 ± 23	0.10
Pa_{O_2}/F_{IO_2} ratio, mm Hg, mean ± SD	211 ± 88	154 ± 67	< 0.001
Expired tidal volume, mL/kg of PBW, median (IQR)	8.3 (6.9–9.5)	9.2 (8.1–12.5)	0.02
Expired tidal volume > 9 mL/kg of PBW, *n*, *n* total	14/47	25/43	< 0.01

IQR = interquartile range, PBW = predicted body weight.

[a]Respiratory rate was collected in 107/110, 104/106, and 91/94 patients, respectively in noninvasive ventilation (NIV), high-flow nasal cannula oxygen, and standard O_2 group; pressure level, positive end-expiratory pressure levels were collected in 103/110 and F_{IO_2} in 108/110 patients in NIV group.

[b]"The intensity of respiratory patient discomfort was collected 1 hour after having started each oxygenation strategy, by use of an unmarked 100 mm Visual Analogic Scale that had ends marked with "no discomfort" and "maximal imaginable discomfort."

after NIV initiation remained independently associated with mortality, aOR 4.51 (95% CI, 1.6–12.6; $p = 0.004$), even after adjustment on severity score (**e-Table 6**, Supplemental Digital Content 1, http://links.lww.com/CCM/C967).

DISCUSSION

This post hoc analysis including patients with acute hypoxemic respiratory failure showed that under standard oxygen, a respiratory rate 1 hour after initiation above 30 breaths/min to be the only predictor of intubation. Under HFNC, no respiratory variable was associated with intubation, and the only predictor of intubation was a high heart rate 1 hour after HFNC initiation. Under NIV, a Pa_{O_2}/F_{IO_2} less than 200 mm Hg and an expired tidal volume exceeding 9 mL/kg of PBW 1 hour after NIV initiation were the two strong predictors of intubation. A high tidal volume 1 hour after NIV initiation remained independently associated with mortality.

Early Predictors of Intubation

Most of the factors predicting intubation previously described, such as severe hypoxemia, shock, or altered consciousness, are themselves intubation criteria (1, 6, 7, 9, 13, 14) and are poor predictors for early decision to intubate. It was previously found that patients with criteria for acute respiratory distress syndrome (ARDS) and severe hypoxemia had an increased risk of intubation as compared to others (7, 14). However,

TABLE 3. Multivariate Logistic Regression Analyses of Factors Associated With Intubation

Risk Factors	OR (95% CI)	*p*
In patients treated with conventional O_2 therapy by nonrebreathing mask[a]		
Respiratory rate ≥ 30 breaths/min at H1	2.76 (1.13–6.75)	0.03
In patients treated with high-flow nasal cannula oxygen therapy[a]		
Heart rate at H1 (per beat/min)	1.03 (1.01–1.06)	< 0.01
In patients treated with noninvasive ventilation[ab]		
Tidal volume > 9 mL/kg of predicted body weight at H1	3.14 (1.22–8.06)	0.02
Pao_2/Fio_2 ≤ 200 mm Hg at H1	4.26 (1.62–11.16)	0.003

[a](c) Index values for the discrimination ability to predict intubation (area under the curve) are 0.634, 0.657, and 0.726, respectively, in conventional O_2 therapy by nonrebreathing mask, high-flow nasal cannula oxygen therapy, and noninvasive ventilation groups.

[b]There was no interaction between tidal volume, Pao_2/Fio_2, and intubation, $p_{interaction} = 0.27$.

Variables entered in the maximal model of logistic regression were as follows:

In patients treated with standard O_2: bilateral pulmonary infiltrates; respiratory rate ≥ 30 breaths/min 1 hr after standard O_2 initiation (at H1), respiratory patient discomfort at H1, heart rate at H1.

In patients treated with high-flow nasal cannula oxygen therapy (HFNC): heart rate 1 hour after HFNC initiation (at H1), systolic arterial pressure at H1, patient discomfort at H1, and class of Pao_2/Fio_2 ratio at H1.

In patients treated with noninvasive ventilation (NIV): immunosuppression status; heart rate 1 hour after NIV initiation (at H1), respiratory rate ≥ 30 breaths/min at H1, class of Pao_2/Fio_2 ratio at H1, and tidal volume exceeding 9 mL/kg of predicted body weight at H1.

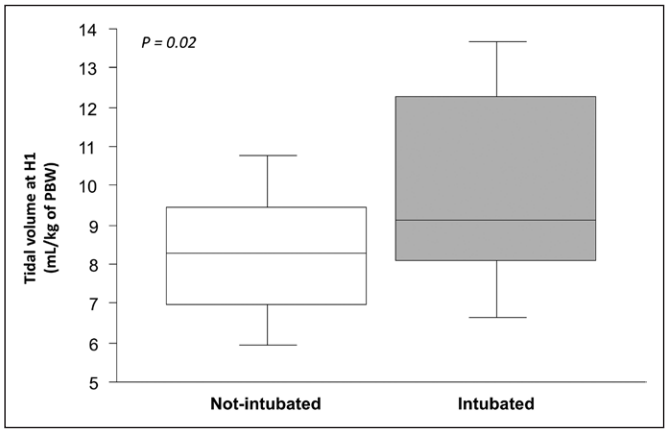

Figure 1. Box plots showing median tidal volumes (25–75th percentiles) in mL/kg of predicted body weight (PBW) 1 hour after noninvasive ventilation initiation in patients who were not intubated (white) and in those who were intubated (gray). The tidal volumes were significantly higher in patients who needed intubation as compared to the others: 8.3 mL/kg (6.9–9.5) of PBW versus 9.2 (8.1–12.5), $p = 0.02$.

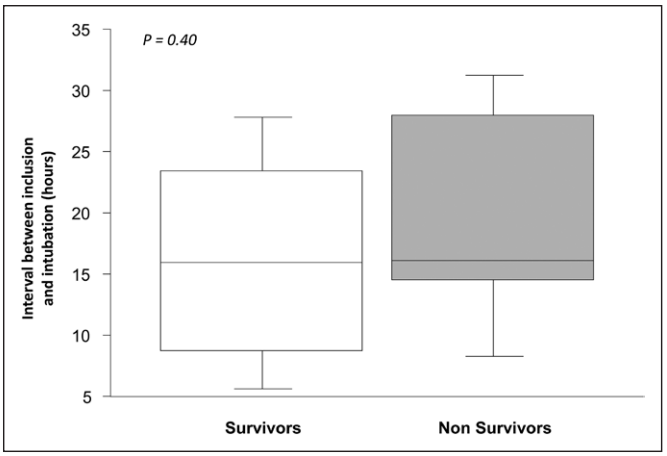

Figure 2. Box plots showing the median delay (25–75th percentiles) in hours between noninvasive ventilation (NIV) initiation and intubation in survivors (white) and nonsurvivors (gray). This delay did not significantly differ between the two groups with a median delay of 16 hr (9–23) versus 16 (15–28) in NIV group ($p = 0.40$).

the patients included in our study and not treated first with mechanical ventilation did not fully fulfill criteria for ARDS. We found that bilateral pulmonary infiltrates at baseline were more frequent in patients who were intubated. However, this variable could not help to predict the need for intubation after initiation of oxygenation strategies while severity of hypoxemia was a predictor of intubation only in patients treated with NIV. Therefore, variables related to severity of the initial disease seem not to be applicable in our study to predict intubation. Rather than factors associated with disease severity, the clinical variables related to response therapy after 1 hour were those that help to predict intubation in the different oxygen delivery strategies.

Predictors of intubation under HFNC have been poorly assessed. It was recently found in an observational study that low ratio of Spo_2/Fio_2-to-respiratory rate was a good predictor of intubation (15). However, this index was calculated after 12 hours of treatment, thereby limiting its interest early in patient management. In our study, no respiratory variable monitored after HFNC initiation was associated with intubation. However, this index was calculated after 12 hours of treatment, thereby limiting its interest early in patient management.

Several studies have suggested that delayed intubation could be associated with higher mortality by masking signs of respiratory distress under NIV (6, 11, 16) as well as under HFNC (10). We did not confirm these results. In our study, the median time to intubation was less than 24 hours after inclusion, and this delay did not differ between survivors and nonsurvivors, either under NIV or under HFNC.

Monitoring Tidal Volume Under NIV

The strategy associating NIV sessions interspaced with HFNC was initially chosen to improve comfort and tolerance under NIV (14, 17) and to preserve a low level of positive pressure under HFNC between two NIV sessions thereby avoiding alveolar derecruitment (18, 19). The poor outcome of patients treated by this strategy seems related to NIV. We observed that patients who needed intubation were more likely to generate high tidal volumes at NIV initiation than those who did not. Pressure-support levels did not differ between the two groups, and therefore, the high tidal volumes generated under NIV were probably the consequence of high respiratory drive and subsequent high patient inspiratory effort. This may reflect a higher severity of the respiratory disease, but patients who needed intubation under NIV did not exhibit higher severity scores or higher respiratory rates than the others, that is, the usual criteria to assess severity at bedside.

As mortality was higher with NIV than with HFNC alone, we cannot exclude that high tidal volumes and subsequent high transpulmonary pressures may, per se, further worsen a preexisting lung insult by inducing superimposed ventilator-induced lung injury (20). Indeed, although barotrauma and worsening of lung injury have been largely demonstrated under invasive mechanical ventilation (21), mechanisms of self-inflicted lung injury due to high transpulmonary pressures may also occur during spontaneous ventilation (22). After multivariate analysis, a tidal volume above 9 mL/kg of PBW was a variable independently associated with intubation. Although we adjusted pressure-support to obtain an expired tidal volume between 7 and 10 mL/kg of PBW, 25% of patients had an expired tidal volume exceeding 10 mL/kg of PBW. Similar findings have recently been reported by Carteaux et al (23) in patients with acute respiratory failure treated with NIV. Although the authors aimed to target a tidal volume between 6 and 8 mL/kg of PBW under NIV, they observed that nearly half of the patients had a tidal volume above 10 mL/kg of PBW. In this study, patients with a tidal volume exceeding 9.5 mL/kg of PBW, a value close to that which we reported, had an increased risk of intubation as compared to the others (23). In our study, a high tidal volume from NIV initiation was also independently associated with mortality, even after adjustment on severity score at admission. It is well established that mortality of patients with ARDS under invasive mechanical ventilation is lower using low tidal volumes approximating 6 mL/kg of PBW (24). Even in patients without strict criteria for ARDS, the use of low tidal volumes may reduce the risk of developing ARDS (25). Although this hypothesis needs to be confirmed by physiologic studies, a better prognosis for patients treated by HFNC alone might result in part from lower tidal volumes and lower levels of transpulmonary pressures (20).

Clinical Implications and Limitations

Obviously, these results do not allow definitive conclusions on the direct impact of tidal volumes under NIV on outcome of patients with acute hypoxemic respiratory failure, but they may help clinicians in the decision process for intubation. Very few studies have assessed the real tidal volumes generated by patients with acute respiratory failure treated with HFNC, and we have not identified any clear early factor predicting HFNC failure. The first limitation of our study is due to the post hoc nature of the analysis and to the tidal volume missing data at NIV initiation (18%). However, our findings came from the largest randomized controlled trial on acute respiratory failure conducted in ICUs. Patients included in the study mainly had severe hypoxemic community-acquired pneumonia without any nonrespiratory organ dysfunction. Therefore, our results may be applicable only to this homogeneous population. Finally, our patients received discontinuous sessions of NIV with relatively low levels of PEEP, and the impact of NIV on outcome might be different using different forms of application of NIV. NIV applied continuously with high PEEP, low pressure-support levels, as recently reported by Patel et al (26) using a helmet, could be safer, but it also needs to be associated with close monitoring of tidal volume to ensure lung protection.

CONCLUSION

In conclusion, a high respiratory rate in patients treated with standard oxygen 1 hour after initiation was a factor associated with intubation in patients with acute hypoxemic respiratory failure, while no respiratory variable was identified to predict HFNC failure. A high tidal volume 1 hour after NIV initiation was independently associated with intubation and remained independently associated with mortality at day 90. When the tidal volume is so elevated, clinicians should be cautious concerning NIV prolongation, which could entail an increased risk of volotrauma.

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REFERENCES

1. Demoule A, Chevret S, Carlucci A, et al; oVNI Study Group; REVA Network (Research Network in Mechanical Ventilation): Changing use of noninvasive ventilation in critically ill patients: Trends over 15 years in francophone countries. *Intensive Care Med* 2016; 42:82–92
2. Ozsancak Ugurlu A, Sidhom SS, Khodabandeh A, et al: Use and outcomes of noninvasive positive pressure ventilation in acute care hospitals in Massachusetts. *Chest* 2014; 145:964–971
3. Papazian L, Corley A, Hess D, et al: Use of high-flow nasal cannula oxygenation in ICU adults: A narrative review. *Intensive Care Med* 2016; 42:1336–1349
4. Antonelli M, Conti G, Esquinas A, et al: A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med* 2007; 35:18–25
5. Schettino G, Altobelli N, Kacmarek RM: Noninvasive positive-pressure ventilation in acute respiratory failure outside clinical trials: Experience at the Massachusetts General Hospital. *Crit Care Med* 2008; 36:441–447
6. Carrillo A, Gonzalez-Diaz G, Ferrer M, et al: Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Med* 2012; 38:458–466
7. Thille AW, Contou D, Fragnoli C, et al: Non-invasive ventilation for acute hypoxemic respiratory failure: Intubation rate and risk factors. *Crit Care* 2013; 17:R269
8. Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group; REVA Network: High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; 372:2185–2196
9. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group: Noninvasive Ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am J Respir Crit Care Med* 2017; 195:67–77
10. Kang BJ, Koh Y, Lim CM, et al: Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med* 2015; 41:623–632
11. Duan J, Han X, Bai L, et al: Assessment of heart rate, acidosis, consciousness, oxygenation, and respiratory rate to predict noninvasive ventilation failure in hypoxemic patients. *Intensive Care Med* 2017; 43:192–199
12. Frat JP, Coudroy R, Ragot S, et al: Acute hypoxemic respiratory failure: Which patients need intubation? *Ann Intensive Care* 2017; 7 (Suppl 1):S10
13. Adda M, Coquet I, Darmon M, et al: Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. *Crit Care Med* 2008; 36:2766–2772
14. Antonelli M, Conti G, Moro ML, et al: Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: A multi-center study. *Intensive Care Med* 2001; 27:1718–1728
15. Roca O, Messika J, Caralt B, et al: Predicting success of high-flow nasal cannula in pneumonia patients with hypoxemic respiratory failure: The utility of the ROX index. *J Crit Care* 2016; 35:200–205
16. Esteban A, Frutos-Vivar F, Ferguson ND, et al: Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004; 350:2452–2460
17. Demoule A; Group. atOS: Understanding noninvasive mechanical ventilation success in French and Belgian ICUs. *Am J Respir Crit Care Med* 2013; 187:A5724
18. Mauri T, Turrini C, Eronia N, et al: Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2017; 195:1207–1215
19. Parke R, McGuinness S, Eccleston M: Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth* 2009; 103: 886–890
20. Slutsky AS, Ranieri VM: Ventilator-induced lung injury. *N Engl J Med* 2014; 370:980
21. de Prost N, Ricard JD, Saumon G, et al: Ventilator-induced lung injury: Historical perspectives and clinical implications. *Ann Intensive Care* 2011; 1:28
22. Brochard L, Slutsky A, Pesenti A: Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017; 195:438–442
23. Carteaux G, Millán-Guilarte T, De Prost N, et al: Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: Role of tidal volume. *Crit Care Med* 2016; 44:282–290
24. Brower RG, Matthay MA, Morris A, et al; Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1301–1308
25. Serpa Neto A, Cardoso SO, Manetta JA, et al: Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: A meta-analysis. *JAMA* 2012; 308:1651–1659
26. Patel BK, Wolfe KS, Pohlman AS, et al: Effect of noninvasive ventilation delivered by helmet vs face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: A randomized clinical trial. *JAMA* 2016; 315:2435–2441