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High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

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ABSTRACT

BACKGROUND

Whether noninvasive ventilation should be administered in patients with acute hypoxemic respiratory failure is debated. Therapy with high-flow oxygen through a nasal cannula may offer an alternative in patients with hypoxemia.

METHODS

We performed a multicenter, open-label trial in which we randomly assigned patients without hypercapnia who had acute hypoxemic respiratory failure and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of 300 mm Hg or less to high-flow oxygen therapy, standard oxygen therapy delivered through a face mask, or noninvasive positive-pressure ventilation. The primary outcome was the proportion of patients intubated at day 28; secondary outcomes included all-cause mortality in the intensive care unit and at 90 days and the number of ventilator-free days at day 28.

RESULTS

A total of 310 patients were included in the analyses. The intubation rate (primary outcome) was 38% (40 of 106 patients) in the high-flow–oxygen group, 47% (44 of 94) in the standard group, and 50% (55 of 110) in the noninvasive-ventilation group ($P=0.18$ for all comparisons). The number of ventilator-free days at day 28 was significantly higher in the high-flow–oxygen group (24±8 days, vs. 22±10 in the standard-oxygen group and 19±12 in the noninvasive-ventilation group; $P=0.02$ for all comparisons). The hazard ratio for death at 90 days was 2.01 (95% confidence interval [CI], 1.01 to 3.99) with standard oxygen versus high-flow oxygen ($P=0.046$) and 2.50 (95% CI, 1.31 to 4.78) with noninvasive ventilation versus high-flow oxygen ($P=0.006$).

CONCLUSIONS

In patients with nonhypercapnic acute hypoxemic respiratory failure, treatment with high-flow oxygen, standard oxygen, or noninvasive ventilation did not result in significantly different intubation rates. There was a significant difference in favor of high-flow oxygen in 90-day mortality. (Funded by the Programme Hospitalier de Recherche Clinique Interrégional 2010 of the French Ministry of Health; FLORALI ClinicalTrials.gov number, NCT01320384.)

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Noninvasive positive-pressure ventilation (hereafter, noninvasive ventilation) reduces the need for endotracheal intubation and mortality among patients with acute exacerbations of chronic obstructive pulmonary disease[1-3] or severe cardiogenic pulmonary edema.[4] The physiological effects of noninvasive ventilation include a decrease in the work of breathing and improvement in gas exchange. In patients with acute hypoxemic respiratory failure, the need for mechanical ventilation is associated with high mortality,[5] but data on the overall effects of noninvasive ventilation with respect to the prevention of intubation and improvement in outcome are conflicting.[6-10]

Previous studies have often included a heterogeneous population of patients with acute respiratory failure who had chronic lung disease[7,10] or cardiogenic pulmonary edema[8,9]; this selection of patients could lead to an overestimation of the beneficial effects of noninvasive ventilation as compared with standard oxygen therapy. In observational studies focusing on patients with acute hypoxemic respiratory failure, the rate of treatment failure with noninvasive ventilation was as high as 50%[11-13] and was often associated with particularly high mortality.[14,15] To date, the literature does not conclusively support the use of noninvasive ventilation in patients with nonhypercapnic acute hypoxemic respiratory failure.

High-flow oxygen therapy through a nasal cannula is a technique whereby heated and humidified oxygen is delivered to the nose at high flow rates. These high flow rates generate low levels of positive pressure in the upper airways, and the fraction of inspired oxygen (F_{IO_2}) can be adjusted by changing the fraction of oxygen in the driving gas.[16-18] The high flow rates may also decrease physiological dead space by flushing expired carbon dioxide from the upper airway, a process that potentially explains the observed decrease in the work of breathing.[19] In patients with acute respiratory failure of various origins, high-flow oxygen has been shown to result in better comfort and oxygenation than standard oxygen therapy delivered through a face mask.[20-25]

To our knowledge, the effect of high-flow oxygen on intubation rate or mortality has not been assessed in patients admitted to the intensive care unit (ICU) with acute hypoxemic respiratory failure. We conducted a prospective, multicenter, randomized, controlled trial involving patients admitted to the ICU with acute hypoxemic respiratory failure to determine whether high-flow oxygen therapy or noninvasive ventilation therapy, as compared with standard oxygen therapy alone, could reduce the rate of endotracheal intubation and improve outcomes.

Methods

Study Oversight

We conducted the study in 23 ICUs in France and Belgium. For all the centers in France, the study protocol (available with the full text of this article at NEJM.org) was approved by the ethics committee at Centre Hospitalier Universitaire de Poitiers; for the study site at Cliniques Universitaires Saint-Luc, Brussels, the protocol was approved by the ethics committee at that center. Written informed consent was obtained from all the patients, their next of kin, or another surrogate decision maker as appropriate.

The trial was overseen by a steering committee that presented information regarding the progression and monitoring of the study at Réseau Européen de Recherche en Ventilation Artificielle (REVA) Network meetings every 4 months. An independent safety monitoring board was set up. Research assistants regularly monitored all the centers on site to check adherence to the protocol and the accuracy of the data recorded. An investigator at each center was responsible for enrolling patients in the study, ensuring adherence to the protocol, and completing the electronic case-report form. Although the individual study assignments of the patients could not be masked, the coordinating center and all the investigators remained unaware of the study-group outcomes until the data were locked in July 2014. All the analyses were performed by the study statistician, in accordance with the International Conference on Harmonisation and Good Clinical Practice guidelines. Face masks, heated humidifiers, and cannulas (i.e., consumable materials) were donated to the participating ICUs, and air-oxygen blenders were provided during the study period, by Fisher and Paykel Healthcare, which had no other involvement in the study.

PATIENTS

Consecutive patients who were 18 years of age or older were enrolled if they met all four of the following criteria: a respiratory rate of more than 25 breaths per minute, a ratio of the partial pressure of arterial oxygen (PaO_2) to the FIO_2 of 300 mm Hg or less while the patient was breathing oxygen at a flow rate of 10 liters per minute or more for at least 15 minutes, a partial pressure of arterial carbon dioxide ($PaCO_2$) not higher than 45 mm Hg, and an absence of clinical history of underlying chronic respiratory failure. FIO_2 was measured by a portable oxygen analyzer (MX300, Teledyne Analytical Instruments) that was introduced in the nonrebreather face mask.

The main exclusion criteria were a $PaCO_2$ of more than 45 mm Hg, exacerbation of asthma or chronic respiratory failure, cardiogenic pulmonary edema, severe neutropenia, hemodynamic instability, use of vasopressors, a Glasgow Coma Scale score of 12 points or less (on a scale from 3 to 15, with lower scores indicating reduced levels of consciousness), contraindications to noninvasive ventilation, urgent need for endotracheal intubation, a do-not-intubate order, and a decision not to participate. Details of the study exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION

Randomization was performed in permuted blocks of six, with stratification according to center and history or no history of cardiac insufficiency. Within 3 hours after the validation of inclusion criteria, patients were randomly assigned in a 1:1:1 ratio, with the use of a centralized Web-based management system (Clinsight, Ennov), to one of the three following strategies: high-flow oxygen therapy, standard oxygen therapy, or noninvasive ventilation.

INTERVENTIONS

In the standard-oxygen group, oxygen therapy was applied continuously through a nonrebreather face mask at a flow rate of 10 liters per minute or more. The rate was adjusted to maintain an oxygen saturation level of 92% or more, as measured by means of pulse oximetry (SpO_2), until the patient recovered or was intubated.

In the high-flow–oxygen group, oxygen was passed through a heated humidifier (MR850, Fisher and Paykel Healthcare) and applied continuously through large-bore binasal prongs, with a gas flow rate of 50 liters per minute and an FIO_2 of 1.0 at initiation (Optiflow, Fisher and Paykel Healthcare). The fraction of oxygen in the gas flowing in the system was subsequently adjusted to maintain an SpO_2 of 92% or more. High-flow oxygen was applied for at least 2 calendar days; it could then be stopped and the patient switched to standard oxygen therapy.

In the noninvasive-ventilation group, noninvasive ventilation was delivered to the patient through a face mask (Fisher and Paykel Healthcare) that was connected to an ICU ventilator, with pressure support applied in a noninvasive-ventilation mode. The pressure-support level was adjusted with the aim of obtaining an expired tidal volume of 7 to 10 ml per kilogram of predicted body weight, with an initial positive end-expiratory pressure (PEEP) between 2 and 10 cm of water. The FIO_2 or PEEP level (or both) were then adjusted to maintain an SpO_2 of 92% or more. The minimally required duration of noninvasive ventilation was 8 hours per day for at least 2 calendar days. Noninvasive ventilation was applied during sessions of at least 1 hour and could be resumed if the respiratory rate was more than 25 breaths per minute or the SpO_2 was less than 92%. Between noninvasive-ventilation sessions, patients received high-flow oxygen, as described above.

STUDY OUTCOMES

The primary outcome was the proportion of patients who required endotracheal intubation within 28 days after randomization. To ensure the consistency of indications across sites and reduce the risk of delayed intubation, the following prespecified criteria for endotracheal intubation were used: hemodynamic instability, a deterioration of neurologic status, or signs of persisting or worsening respiratory failure as defined by at least two of the following criteria: a respiratory rate of more than 40 breaths per minute, a lack of improvement in signs of high respiratory-muscle workload, the development of copious tracheal secretions, acidosis with a pH of less than 7.35, an SpO_2 of less than 90% for more than 5 minutes without technical dysfunction, or a poor response to oxygenation techniques (details of the criteria are provided in the Supplementary Appendix). In

the high-flow–oxygen group and the standard-oxygen group, a trial of noninvasive ventilation was allowed at the discretion of the physician in patients who had signs of persisting or worsening respiratory failure and no other organ dysfunction before endotracheal intubation was performed and invasive ventilation initiated.

Secondary outcomes were mortality in the ICU, mortality at 90 days, the number of ventilator-free days (i.e., days alive and without invasive mechanical ventilation) between day 1 and day 28, and the duration of ICU stay. Other prespecified outcomes included complications during the ICU stay, such as septic shock, nosocomial pneumonia, cardiac arrhythmia, and cardiac arrest. Dyspnea was assessed with the use of a 5-point Likert scale, and comfort with the use of a 100-mm visual-analogue scale (see the Supplementary Appendix).

STATISTICAL ANALYSIS

Assuming an intubation rate of 60% in the population that was treated with standard oxygen therapy,[7,9,10] we calculated that enrollment of 300 patients would provide the study with 80% power to show an absolute difference of 20 percentage points in the primary outcome between the standard-oxygen group and either the high-flow–oxygen group or the noninvasive-ventilation group at a two-sided alpha level of 0.05.

All the analyses were performed on an intention-to-treat basis. Kaplan–Meier curves were plotted to assess the time from enrollment to endotracheal intubation or death and were compared by means of the log-rank test.

The treatment (standard oxygen, high-flow oxygen, or noninvasive ventilation) was introduced as two dummy variables to obtain two odds ratios or hazard ratios for comparison with the reference group, which was defined as the lowest-risk group. Variables associated with intubation at day 28 and in-ICU mortality were assessed by means of multivariate logistic-regression analyses, and those associated with mortality at 90 days were assessed by means of a Cox proportional-hazard regression analysis with the use of a backward-selection procedure. The final model included a history of cardiac insufficiency and variables significantly associated with intubation or mortality with a P value of less than 0.05.

We conducted only one post hoc subgroup analysis, which included patients with a Pao_2:FIO_2 of 200 mm Hg or less at enrollment, to analyze outcomes in patients with severe hypoxemia. This threshold of the Pao_2:FIO_2 was based on the classification of the acute respiratory distress syndrome.[26-28]

A two-tailed P value of less than 0.05 was considered to indicate statistical significance. We used SAS software, version 9.2 (SAS Institute), for all the analyses.

RESULTS

PATIENTS

From February 2011 through April 2013, a total of 2506 patients with acute hypoxemic respiratory failure were admitted to the 23 participating ICUs; 525 patients were eligible for inclusion in the study, and 313 underwent randomization (Fig. 1). After the secondary exclusion of 3 patients who withdrew consent, 310 patients were included in the analysis. A total of 94 patients were assigned to standard oxygen therapy, 106 to high-flow oxygen therapy, and 110 to noninvasive ventilation. The median interval between randomization and the initiation of treatment was 60 minutes (interquartile range, 11 to 120).

CHARACTERISTICS AT INCLUSION

The characteristics of the patients at enrollment were similar in the three groups (Table 1). The main cause of acute respiratory failure was community-acquired pneumonia, which was the diagnosis in 197 patients (64%). Bilateral pulmonary infiltrates were present in 244 patients (79%), and 238 patients (77%) had a Pao_2:FIO_2 of 200 mm Hg or less at the time of enrollment (Tables S1 and S3 in the Supplementary Appendix). The mean (±SD) baseline FIO_2, as measured through the nonrebreather face mask in 286 patients, was 0.65±0.13.

TREATMENTS

The initial mean settings were as follows: in the standard-oxygen group, an oxygen flow rate of 13±5 liters per minute; in the high-flow–oxygen group, a gas flow rate of 48±11 liters per minute, yielding a mean FIO_2 of 0.82±0.21; and in the noninvasive-ventilation group, a pressure-sup-

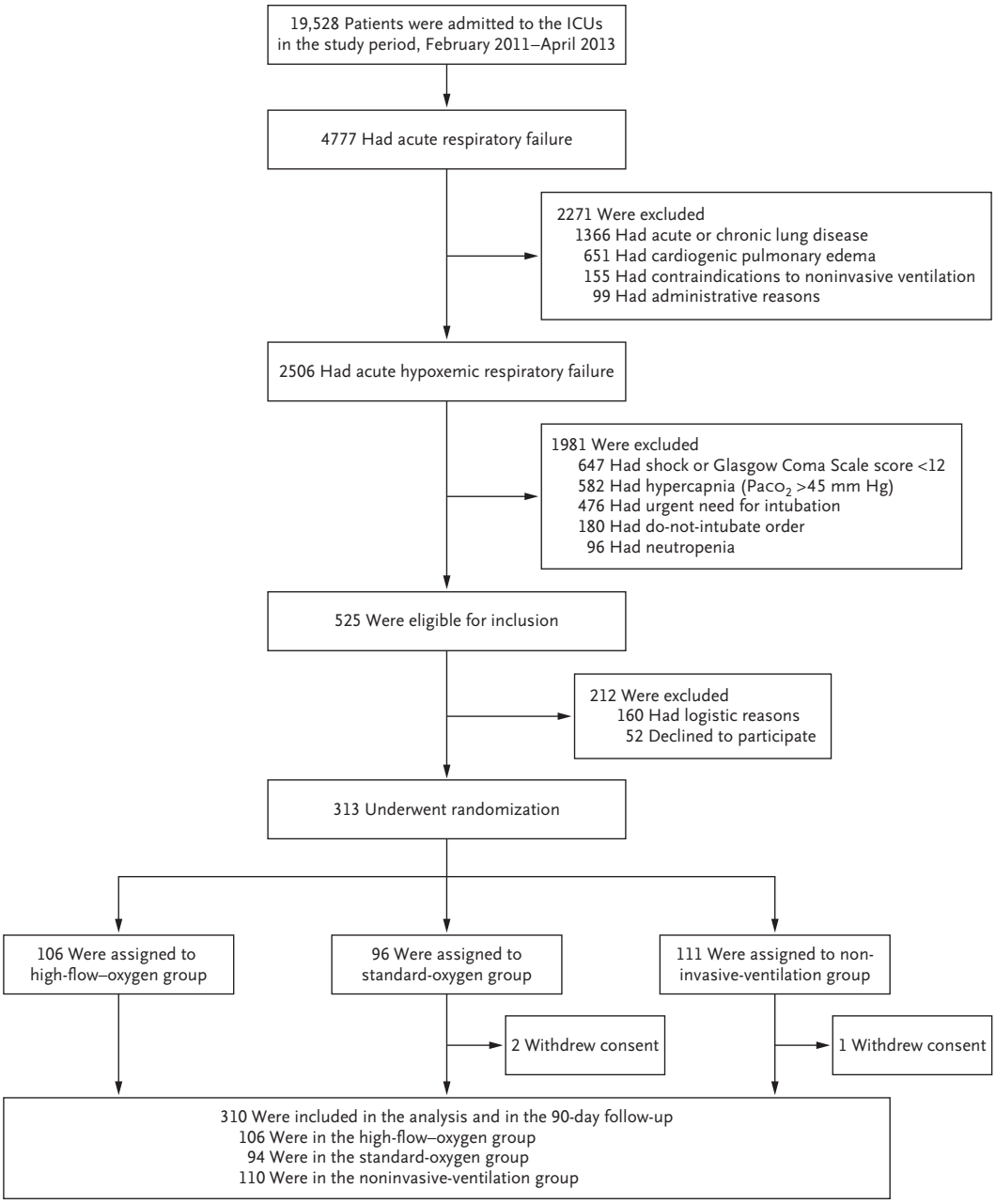


Figure 1. Enrollment, Randomization, and Follow-up of the Study Participants.

High-flow oxygen indicates therapy with high-flow oxygen through a nasal cannula. Patients who were assigned to receive noninvasive positive-pressure ventilation (hereafter, noninvasive ventilation) received noninvasive ventilation and high-flow oxygen between sessions of noninvasive ventilation. Standard oxygen therapy was given through a non-rebreather face mask at a flow rate of 10 liters or more per minute. Patients may have had more than one reason for exclusion from the trial. Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating reduced levels of consciousness. ICU denotes intensive care unit, and $Paco_2$ partial pressure of arterial carbon dioxide.

Table 1. Characteristics of the Patients at Baseline, According to Study Group.*

Characteristic	High-Flow Oxygen (N=106)	Standard Oxygen (N=94)	Noninvasive Ventilation (N=110)
Age — yr	61±16	59±17	61±17
Male sex — no. (%)	75 (71)	63 (67)	74 (67)
Body-mass index†	25±5	26±5	26±6
SAPS II‡	25±9	24±9	27±9
Current or past smoking — no. (%)	34 (32)	36 (38)	40 (36)
Reason for acute respiratory failure — no. (%)			
Community-acquired pneumonia	71 (67)	57 (61)	69 (63)
Hospital-acquired pneumonia	12 (11)	13 (14)	12 (11)
Extrapulmonary sepsis	4 (4)	5 (5)	7 (6)
Aspiration or drowning	3 (3)	1 (1)	2 (2)
Pneumonia related to immunosuppression	6 (6)	4 (4)	10 (9)
Other	10 (9)	14 (15)	10 (9)
Bilateral pulmonary infiltrates — no. (%)	79 (75)	80 (85)	85 (77)
Respiratory rate — breaths/min	33±6	32±6	33±7
Heart rate — beats/min	106±21	104±16	106±21
Arterial pressure — mm Hg			
Systolic	127±24	130±22	128±21
Mean	87±17	89±15	86±16
Arterial blood gas			
pH	7.43±0.05	7.44±0.06	7.43±0.06
Pao_2 — mm Hg	85±31	92±32	90±36
FIO_2§	0.62±0.19	0.63±0.17	0.65±0.15
Pao_2:FIO_2 — mm Hg	157±89	161±73	149±72
$Paco_2$ — mm Hg	36±6	35±5	34±6

* Plus–minus values are means ±SD. There were no significant differences among the study groups in any of the characteristics listed. High-flow oxygen indicates therapy with high-flow oxygen through a nasal cannula. Patients who were assigned to receive noninvasive positive-pressure ventilation (hereafter, noninvasive ventilation) received noninvasive ventilation and high-flow oxygen between sessions of noninvasive ventilation. Standard oxygen therapy was given through a nonrebreather face mask at a flow rate of 10 liters or more per minute. FIO_2 denotes fraction of inspired oxygen, $Paco_2$ partial pressure of arterial carbon dioxide, and Pao_2 partial pressure of arterial oxygen.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The Simplified Acute Physiology Score (SAPS) II was calculated from 17 variables at enrollment, information about previous health status, and information obtained at admission. Scores range from 0 to 163, with higher scores indicating more severe disease.

§ FIO_2 was measured in 286 patients and was estimated in the remaining patients as follows: (oxygen flow in liters per minute) × 0.3 + 0.21.

port level of 8±3 cm of water, a PEEP of 5±1 cm of water, and an FIO_2 of 0.67±0.24, resulting in a tidal volume of 9.2±3.0 ml per kilogram. Noninvasive ventilation was delivered for 8 hours (interquartile range, 4 to 12) on day 1 and for 8 hours (interquartile range, 4 to 13) on day 2.

PRIMARY AND SECONDARY OUTCOMES

The intubation rate at day 28 was 38% in the high-flow–oxygen group, 47% in the standard-oxygen group, and 50% in the noninvasive-ventilation group (P=0.18; P=0.17 by the log-rank test) (Fig. 2A). The intervals between enrollment

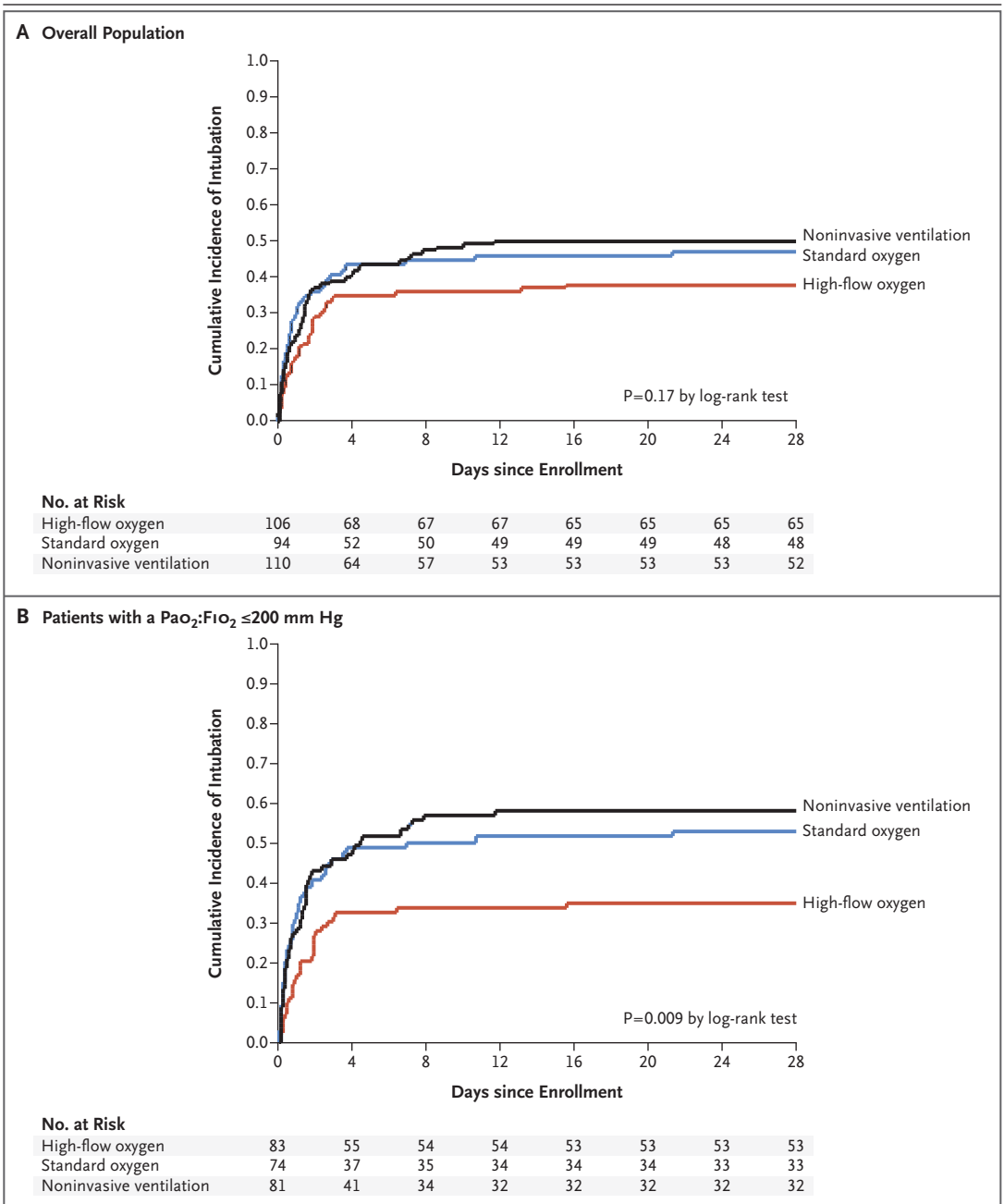


Figure 2. Kaplan–Meier Plots of the Cumulative Incidence of Intubation from Randomization to Day 28.

Results in the overall population and in patients with a Pao_2:FIO_2 of 200 mm Hg or less are shown. Pao_2:FIO_2 denotes the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen.

and intubation, as well as the reasons for intubation, did not differ significantly among the three groups (Table 2).

The crude in-ICU mortality and 90-day mortality differed significantly among the three groups (Table 2 and Fig. 3). The hazard ratio for death at 90 days was 2.01 (95% confidence interval [CI], 1.01 to 3.99) in the standard-oxygen

group as compared with the high-flow–oxygen group (P=0.046) and 2.50 (95% CI, 1.31 to 4.78) in the noninvasive-ventilation group as compared with the high-flow–oxygen group (P=0.006; P=0.02 by the log-rank test) (Fig. 3). The risk of death at 90 days remained significantly lower in the high-flow–oxygen group after adjustment for the baseline Simplified Acute Physiology Score II and history of cardiac insufficiency (Table 2). Four patients died in the ICU without having undergone intubation (two in the standard-oxygen group and one in each of the other two groups). The 90-day mortality among patients who required intubation did not differ significantly among the groups (Table 2). The number of ventilator-free days at day 28 was significantly higher in the high-flow–oxygen group than in the other two groups (Table 2).

In a post hoc analysis, there was a significant interaction between the Pao_2:FIO_2 at enrollment (≤200 mm Hg vs. >200 mm Hg) and the treatment group with respect to status regarding intubation (P=0.01). In the subgroup of patients with a Pao_2:FIO_2 of 200 mm Hg or less, the intubation rate was significantly lower in the high-flow–oxygen group than in the other two groups (Fig. 2B and Table 2, and Table S4 in the Supplementary Appendix). The risk of intubation remained significantly lower in the high-flow–oxygen group after adjustment for bilateral pulmonary infiltrates, respiratory rate, and preexisting history of cardiac insufficiency.

Table 2. Primary and Secondary Outcomes, According to Study Group.*

Outcome	Study Group			P Value†	Odds Ratio or Hazard Ratio (95% CI)	
	High-Flow Oxygen (N=106)	Standard Oxygen (N=94)	Noninvasive Ventilation (N=110)		Standard Oxygen vs. High-Flow Oxygen	Noninvasive Ventilation vs. High-Flow Oxygen
Intubation at day 28						
Overall population				0.18	1.45 (0.83–2.55)	1.65 (0.96–2.84)
No. of patients	40	44	55			
% of patients (95% CI)	38 (29–47)	47 (37–57)	50 (41–59)			
Patients with Pao_2:FIO_2 ≤200 mm Hg‡						
Unadjusted analysis				0.009	2.07 (1.09–3.94)	2.57 (1.37–4.84)
No. of patients/total no.	29/83	39/74	47/81			
% of patients (95% CI)	35 (26–46)	53 (42–64)	58 (47–68)			
Adjusted analysis§	—	—	—	0.01	2.14 (1.08–4.22)	2.60 (1.36–4.96)
Interval between enrollment and intubation — hr¶						
Overall population				0.27	—	—
Median	27	15	27			
Interquartile range	8–46	5–39	8–53			
Patients with Pao_2:FIO_2 ≤200 mm Hg				0.32	—	—
Median	26	17	27			
Interquartile range	11–46	5–41	7–52			
Reason for intubation — no./total no. (%)‖						
Respiratory failure	36/51 (71)	43/58 (74)	49/67 (73)	0.24	—	—
Circulatory failure	7/51 (14)	5/58 (9)	5/67 (7)	0.46	—	—
Neurologic failure	8/51 (16)	10/58 (17)	13/67 (19)	0.91	—	—
Ventilator-free days						
Overall population	24±8	22±10	19±12	0.02	—	—
Patients with Pao_2:FIO_2 ≤200 mm Hg	24±8	21±10	18±12	<0.001	—	—

Table 2. (Continued.)

Outcome	Study Group			P Value†	Odds Ratio or Hazard Ratio (95% CI)	
	High-Flow Oxygen (N=106)	Standard Oxygen (N=94)	Noninvasive Ventilation (N=110)		Standard Oxygen vs. High-Flow Oxygen	Noninvasive Ventilation vs. High-Flow Oxygen
Death						
In ICU						
Unadjusted analysis				0.047	1.85 (0.84–4.09)	2.55 (1.21–5.35)
No. of patients	12	18	27			
% of patients (95% CI)	11 (6–19)	19 (12–28)	25 (17–33)			
Adjusted analysis**	—	—	—	—	2.55 (1.07–6.08)	2.60 (1.20–5.63)
At day 90						
Overall population						
Unadjusted analysis				0.02	2.01 (1.01–3.99)	2.50 (1.31–4.78)
No. of patients	13	22	31			
% of patients (95% CI)	12 (7–20)	23 (16–33)	28 (21–37)			
Adjusted analysis**	—	—	—	—	2.36 (1.18–4.70)	2.33 (1.22–4.47)
Intubated patients				0.16		
No. of patients/total. no.	12/40	20/44	27/55			
% of patients (95% CI)	30 (18–46)	45 (32–60)	49 (36–62)			
Cause of death — no./total no. (%)						
Refractory shock	6/13 (46)	12/22 (55)	18/31 (58)	0.04		
Refractory hypoxemia	5/13 (38)	6/22 (27)	8/31 (26)	0.73		
Cardiac arrest	1/13 (8)	1/22 (5)	3/31 (10)	0.52		
Other	1/13 (8)	3/22 (14)	2/31 (6)	0.52		

* Plus–minus values are means ±SD. Hazard ratios are shown for mortality at day 90, and odds ratios are shown for other outcomes. For the comparisons, the high-flow–oxygen group was used as the reference group because that group was the lowest-risk group. The number of ventilator-free days was defined as the number of days without invasive mechanical ventilation at day 28; for patients who died, 0 days were assigned. CI denotes confidence interval.

† P values are for the three-group comparison.

‡ The interaction between treatment and Pao_2:FIo_2 with respect to status regarding intubation was significant (P=0.01) in the subgroup of patients with a Pao_2:FIo_2 of 200 mm Hg or less. Intubation rates at day 28 did not differ significantly among the treatment groups in the subgroup of patients with a Pao_2:FIo_2 of more than 200 mm Hg.

§ The analysis was adjusted for bilateral pulmonary infiltrates, respiratory rate, and preexisting history of cardiac insufficiency.

¶ The values for the interval between enrollment and intubation include data for the 139 intubated patients in the overall population and the 115 intubated patients in the subgroup of patients with a Pao_2:FIo_2 of more than 200 mm Hg.

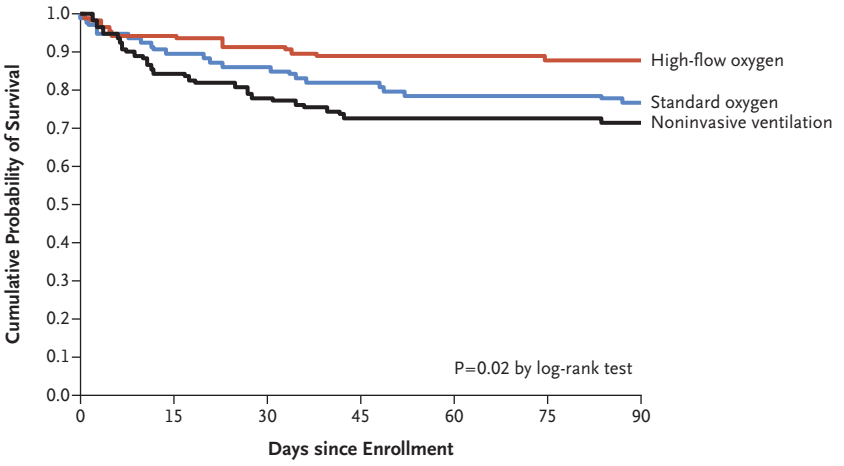
‖ No deviation was observed in the prespecified criteria for intubation, and no patient was intubated who did not meet these criteria.

** The analysis was adjusted for SAPS II and history of cardiac insufficiency.

The rate of various complications during the ICU stay did not differ significantly among the groups (Tables S2 and S4 in the Supplementary Appendix). Among the 40 patients who received noninvasive ventilation as rescue therapy, 19 of 26 patients (73%) in the standard-oxygen group and 9 of 14 (64%) in the high-flow–oxygen group were intubated subsequently.

PATIENT COMFORT AND SAFETY

At 1 hour after enrollment, the intensity of respiratory discomfort in the patients was reduced and the dyspnea score was improved with the use of high-flow oxygen, as compared with the other two strategies of oxygenation (Table S5 in the Supplementary Appendix). There was no significant difference among the groups in the overall



No. at Risk							
High-flow oxygen	106	100	97	94	94	93	93
Standard oxygen	94	84	81	77	74	73	72
Noninvasive ventilation	110	93	86	80	79	78	77

Figure 3. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

incidence of serious adverse events. Among the 18 episodes of cardiac arrest, 3 occurred before intubation (1 in the standard-oxygen group and 2 in the high-flow–oxygen group). Two patients died during the process of intubation.

DISCUSSION

In this multicenter, randomized, open-label trial, neither noninvasive ventilation nor high-flow oxygen decreased the rate of intubation (the primary outcome) among patients with acute hypoxemic respiratory failure. High-flow oxygen therapy, as compared with standard oxygen therapy or noninvasive ventilation, resulted in reduced mortality in the ICU and at 90 days.

When planning the study, we assumed an intubation rate of 60% in the standard-oxygen group on the basis of data from previous randomized, controlled trials.[7,9,10] Our results showed a lower rate than expected in the standard-oxygen group (47%) but also a higher rate than expected among patients treated with noninvasive ventilation (50%). The intubation rate in the noninvasive-ventilation group in our study is, however, consistent with the rates of 46 to 54% observed in other studies that included patients with acute hypoxemic respiratory failure.[11-13,29] In a few observational studies,[21,24,30] lower rates of intubation were seen among patients with hypoxemia who were receiving high-flow oxygen therapy than among those receiving noninvasive ventilation or standard oxygen therapy.

The lower mortality observed in the high-flow–oxygen group may have resulted from the cumulative effects of less intubation particularly in the patients with severe hypoxemia (PaO_2:FIO_2 ≤200 mm Hg), as compared with other patients, and a slightly lower mortality among intubated patients who were treated with high-flow oxygen therapy than among those who were treated with one of the other strategies (Table 2). Two studies have also suggested that a failure of noninvasive ventilation might result in excess mortality, possibly because of delayed intubation,[12,31] but we found no significant difference among the groups in terms of the time until intubation or the reasons for intubation. In our study, noninvasive ventilation that was administered to patients with severe lung injury could have increased the incidence of ventilator-induced lung injury by increasing tidal volumes that exceeded 9 ml per kilogram of predicted body weight.[32-34] High-flow oxygen was also associated with an increased degree of comfort, a reduction in the severity of dyspnea, and a decreased respiratory

rate. These findings might result from the heating and humidification of inspired gases, which prevented thick secretions and subsequent atelectasis but also from low levels of PEEP generated by a high gas flow rate[16,17] and flushing of upper-airway dead space.[20,21,23,24]

Our trial had several strengths that suggest that the results may be generalized to patients admitted for nonhypercapnic acute hypoxemic respiratory failure in other ICUs. These strengths included the multicenter design and sealed randomization to the assigned strategy, a well-defined study protocol that included prespecified criteria for intubation, complete follow-up at 90 days, and an intention-to-treat analysis.

The main limitation of our study was the low power to detect a significant between-group difference in the intubation rate in the overall population. A reduced intubation rate was detected in the post hoc analysis in the subgroup of patients with a PaO_2:FIO_2 of 200 mm Hg or less, which was justified by a significant interaction between PaO_2:FIO_2 stratum and treatment.[35]

In conclusion, treatment with high-flow oxygen improved the survival rate among patients with acute hypoxemic respiratory failure, even though no difference in the primary outcome (i.e., intubation rate) was observed with high-flow oxygen therapy, as compared with standard oxygen therapy or noninvasive ventilation.

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APPENDIX

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REFERENCES

1. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 1995;333:817-22.
2. Keenan SP, Sinuff T, Cook DJ, Hill NS. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. Ann Intern Med 2003;138:861-70.
3. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ 2003;326:185.
4. Masip J, Roque M, Sánchez B, Fernández R, Subirana M, Expósito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. JAMA 2005;294:3124-30.
5. Esteban A, Frutos-Vivar F, Muriel A, et al. Evolution of mortality over time in patients receiving mechanical ventilation. Am J Respir Crit Care Med 2013;188:220-30.
6. Wysocki M, Tric L, Wolff MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure: a randomized comparison with conventional therapy. Chest 1995;107:761-8.
7. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Umberto Meduri G. Acute respiratory failure in patients with severe community-acquired pneumonia: a prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med 1999;160:1585-91.
8. Delclaux C, L'Her E, Alberti C, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. JAMA 2000;284:2352-60.
9. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med 2003;168:1438-44.

10. Martin TJ, Hovis JD, Costantino JP, et al. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. Am J Respir Crit Care Med 2000;161:807-13.
11. 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.
12. 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;38:458-66.
13. Thille AW, Contou D, Fragnoli C, Córdoba-Izquierdo A, Boissier F, Brun-Buisson C. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. Crit Care 2013;17:R269.
14. Demoule A, Girou E, Richard JC, Taille S, Brochard L. Benefits and risks of success or failure of noninvasive ventilation. Intensive Care Med 2006;32:1756-65.
15. 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;36:441-7.
16. Chanques G, Riboulet F, Molinari N, et al. Comparison of three high flow oxygen therapy delivery devices: a clinical physiological cross-over study. Minerva Anestesiol 2013;79:1344-55.
17. Corley A, Caruana LR, Barnett AG, Tronstad O, Fraser JF. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. Br J Anaesth 2011;107:998-1004.
18. Parke RL, Eccleston ML, McGuinness SP. The effects of flow on airway pressure during nasal high-flow oxygen therapy. Respir Care 2011;56:1151-5.
19. Pham TM, O'Malley L, Mayfield S, Martin S, Schibler A. The effect of high flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. Pediatr Pulmonol 2014 May 21 (Epub ahead of print).
20. Cuquemelle E, Pham T, Papon JF, Louis B, Danin PE, Brochard L. Heated and humidified high-flow oxygen therapy reduces discomfort during hypoxemic respiratory failure. Respir Care 2012;57:1571-7.
21. Frat JP, Brugiere B, Ragot S, et al. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. Respir Care 2015;60:170-8.
22. Maggiore SM, Idone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation: effects on oxygenation, comfort, and clinical outcome. Am J Respir Crit Care Med 2014;190:282-8.
23. Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. Respir Care 2010;55:408-13.
24. Sztrymf B, Messika J, Bertrand F, et al. Beneficial effects of humidified high flow nasal oxygen in critical care patients: a prospective pilot study. Intensive Care Med 2011;37:1780-6.
25. Sztrymf B, Messika J, Mayot T, Lenglet H, Dreyfuss D, Ricard JD. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: a prospective observational study. J Crit Care 2012;27(3):324.e9-324.e13.
26. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818-24.
27. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. Intensive Care Med 2012;38:1573-82.
28. ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.
29. 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;145:964-71.
30. Messika J, Ben Ahmed K, Gaudry S, et al. Use of high-flow nasal cannula oxygen therapy in subjects with ARDS: a 1-year observational study. Respir Care 2015;60:162-9.
31. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 2004;350:2452-60.
32. Dreyfuss D, Saumon G. Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. Am Rev Respir Dis 1993;148:1194-203.
33. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2014;370:980.
34. de Prost N, Ricard JD, Saumon G, Dreyfuss D. Ventilator-induced lung injury: historical perspectives and clinical implications. Ann Intensive Care 2011;1:28.
35. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine — reporting of subgroup analyses in clinical trials. N Engl J Med 2007;357:2189-94.