EDITORIAL

Saving Lives with High-Flow Nasal Oxygen

Michael A. Matthay, M.D.

First reported in 1890,[1] therapy with oxygen constitutes one of the fundamental advances in clinical medicine. It is an essential treatment for acute and chronic respiratory failure, a supportive therapy for general anesthesia and most surgical procedures, and an adjunctive treatment for patients with shock from sepsis, trauma, or cardiac failure.

For spontaneously breathing patients with acute respiratory failure, various methods for providing supplemental oxygen have been studied. Noninvasive positive-pressure ventilation with a tight-fitting face mask reduces morbidity and mortality among selected patients with acute respiratory failure caused by an exacerbation of chronic obstructive pulmonary disease.[2,3] Noninvasive ventilation also has proven value in some patients with hypoxemia from cardiogenic pulmonary edema.[4]

However, among commonly used approaches, the best option for patients with acute hypoxemic respiratory failure remains uncertain. In the past decade, high-flow oxygen delivered through a nasal cannula has emerged as an alternative to noninvasive ventilation or oxygen delivered through a face mask.[5] This form of delivery provides a high concentration of heated and humidified oxygen through a nasal cannula, with flow rates from 40 to 60 liters per minute that generate low levels of positive end-expiratory pressure. It is thought to be more comfortable for the patient than the other strategies and may reduce the work of breathing; importantly, it increases the excretion of carbon dioxide.[5,6] Some studies have shown a potential role for high-flow oxygen in supporting patients with hypoxemia after extubation[7] and in treating newborn infants with respiratory distress.[5] However, randomized trials to compare the efficacy of high-flow oxygen with other oxygen-delivery systems in patients with acute hypoxemic respiratory failure have been lacking.

Frat et al.[8] now report in the *Journal* the results of a randomized, multicenter trial involving 310 patients that was designed to assess clinical outcomes with high-flow oxygen, noninvasive ventilation, and standard oxygen therapy for acute, nonhypercapnic, hypoxemic respiratory failure (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [Pa_{O_2}:F_{IO_2}], ≤300 mm Hg); the acute respiratory failure was caused predominantly by pneumonia. The primary outcome, the rate of endotracheal intubation, was lower among patients treated with high-flow oxygen than among those who received standard oxygen therapy or noninvasive ventilation, but the rates did not differ significantly (38% vs. 47% and 50%, respectively) ($P=0.18$). However, in a post hoc adjusted analysis that included the 238 patients with severe initial hypoxemia (Pa_{O_2}:F_{IO_2}, ≤200 mm Hg), the intubation rate was significantly lower among patients who received high-flow oxygen than among patients in the other two groups ($P=0.009$).

In the entire cohort of 310 patients, the high-flow delivery mode significantly increased the number of ventilator-free days and also reduced 90-day mortality, as compared with standard oxygen therapy alone ($P=0.046$) or noninvasive ventilation ($P=0.006$). As compared with the other strategies, high-flow oxygen was associated with less respiratory discomfort and a reduction in the severity of dyspnea, as measured by validated assessments of patient comfort. It appears that the system for delivering high-flow oxygen through a nasal cannula decreased the pulmonary dead space, as indicated by a lower respiratory rate than was observed with the other strategies at the same partial pressure of arterial carbon dioxide ($Paco_2$) (Table S5 in the Supplementary Appendix, available with the full text of the article at NEJM.org). This finding is important because elevated pulmonary dead space contributes to increased mortality among patients with acute respiratory failure from arterial hypoxemia and the acute respiratory distress syndrome.[9]

The trial had several strengths. The baseline characteristics in the three groups were well matched, the use of intubation was guided by sound prespecified criteria, and patients underwent randomization within 3 hours after qualifying for the trial. The trial excluded patients with a history of chronic respiratory failure including a $Paco_2$ of more than 45 mm Hg, and stratification was performed according to study center and a history of cardiac disease.

There were some limitations. By necessity, the trial could not be blinded, and some patients were allowed to cross over to noninvasive ventilation if they did not have a good response to standard oxygen therapy or high-flow oxygen therapy, although the number of crossovers was small. The total number of patients enrolled for a three-group trial was modest (310 patients), and the trial was really a negative trial, because the primary outcome of intubation rate did not reach significance and the significantly reduced rate of intubation among the 238 patients with severe hypoxemia was not a prespecified outcome.

Nevertheless, and remarkably, therapy with high-flow oxygen significantly reduced 90-day mortality. Why? Since the mean tidal volume in the noninvasive-ventilation group was greater than 9 ml per kilogram of predicted body weight, the degree of lung injury might have been increased in this group, contributing to a higher mortality than that observed in the high-flow oxygen group.[10] Alternatively, because the rate of death from shock was significantly lower among patients treated with high-flow oxygen than among those treated with one of the other strategies, there may have been better containment of the microbial and inflammatory components of pneumonia to the lung because of the reduced need for endotracheal intubation and positive-pressure ventilation, especially in patients with severe hypoxemia.

I believe that high-flow oxygen therapy through a nasal cannula should be considered to be an effective and safe therapy for the treatment of spontaneously breathing patients with acute hypoxemic respiratory failure. Although additional trials are needed, high-flow oxygen should be used for the treatment of patients without hypercapnia and with acute severe hypoxemic respiratory failure in the emergency department, the intensive care unit, and hospital settings in which appropriate monitoring is available.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

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 (Pa_{O_2}) to the F_{IO_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 (Pa_{CO_2}) not higher than 45 mm Hg, and an absence of clinical history of underlying chronic respiratory failure. F_{IO_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 Pa_{CO_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 (Sp_{O_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 F_{IO_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 Sp_{O_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 F_{IO_2} or PEEP level (or both) were then adjusted to maintain an Sp_{O_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 Sp_{O_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 Sp_{O_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 Pa_{O_2}:F_{IO_2} of 200 mm Hg or less at enrollment, to analyze outcomes in patients with severe hypoxemia. This threshold of the Pa_{O_2}:F_{IO_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 Pa_{O_2}:F_{IO_2} of 200 mm Hg or less at the time of enrollment (Tables S1 and S3 in the Supplementary Appendix). The mean (±SD) baseline F_{IO_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 F_{IO_2} of 0.82±0.21; and in the noninvasive-ventilation group, a pressure-sup-

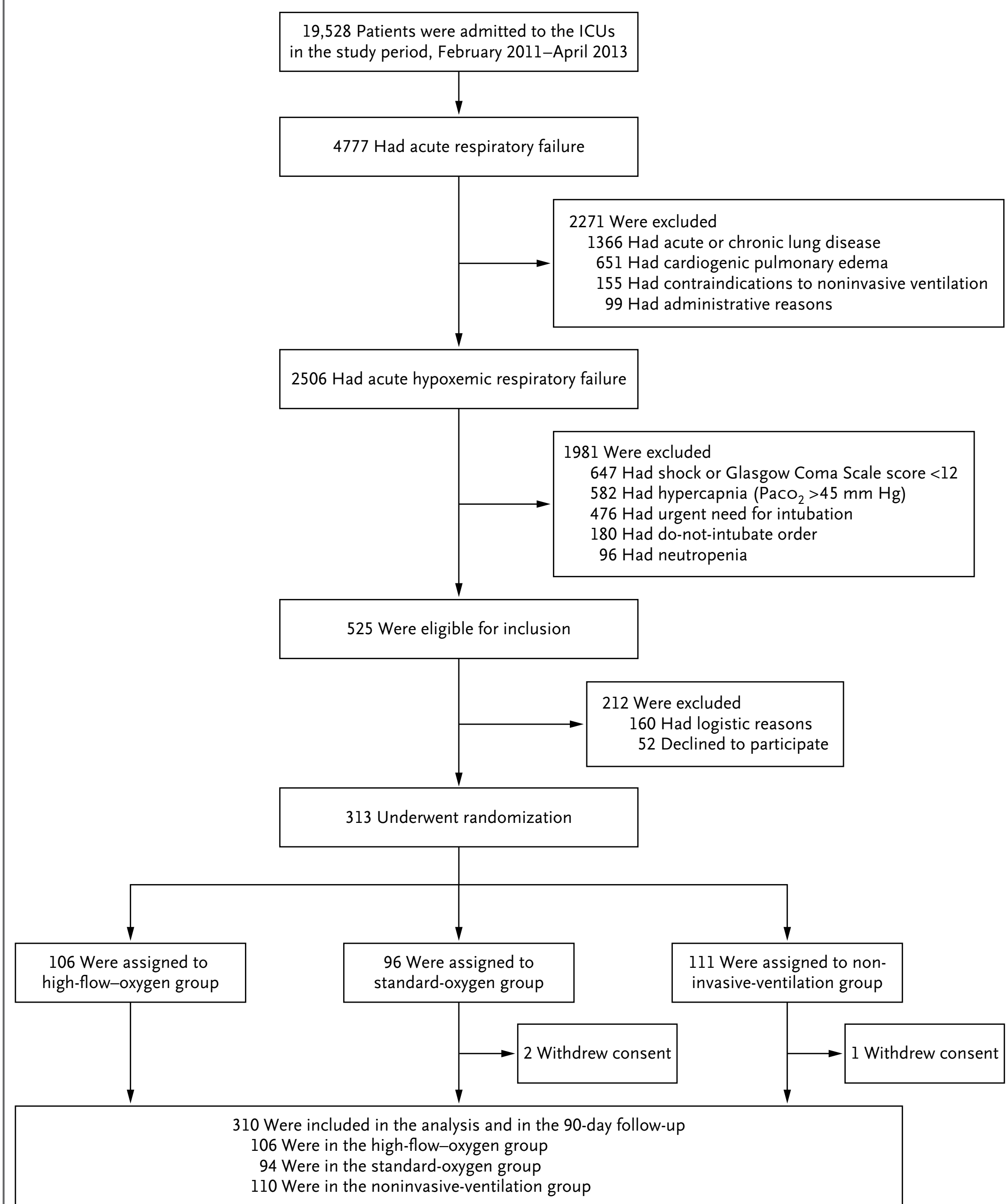


Figure 1. Enrollment, Randomization, and Follow-up of the Study Participants.

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 nonrebreather 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
Pa_{O_2} — mm Hg	85±31	92±32	90±36
FI_{O_2}§	0.62±0.19	0.63±0.17	0.65±0.15
Pa_{O_2}:FI_{O_2} — mm Hg	157±89	161±73	149±72
Pa_{CO_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. FI_{O_2} denotes fraction of inspired oxygen, Pa_{CO_2} partial pressure of arterial carbon dioxide, and Pa_{O_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.

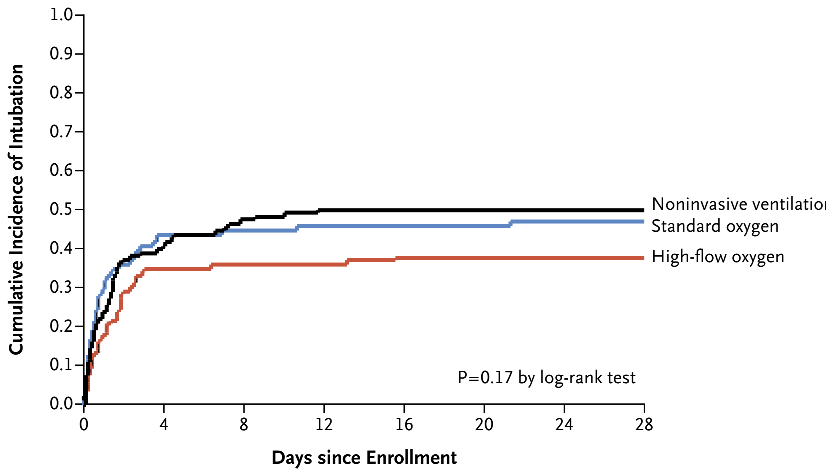
§ FI_{O_2} was measured in 286 patients and was estimated in the remaining patients as follows: (oxygen flow in liters per minute) × 0.3 + 0.21.

port level of 8±3 cm of water, a PEEP of 5±1 cm of water, and an FI_{O_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

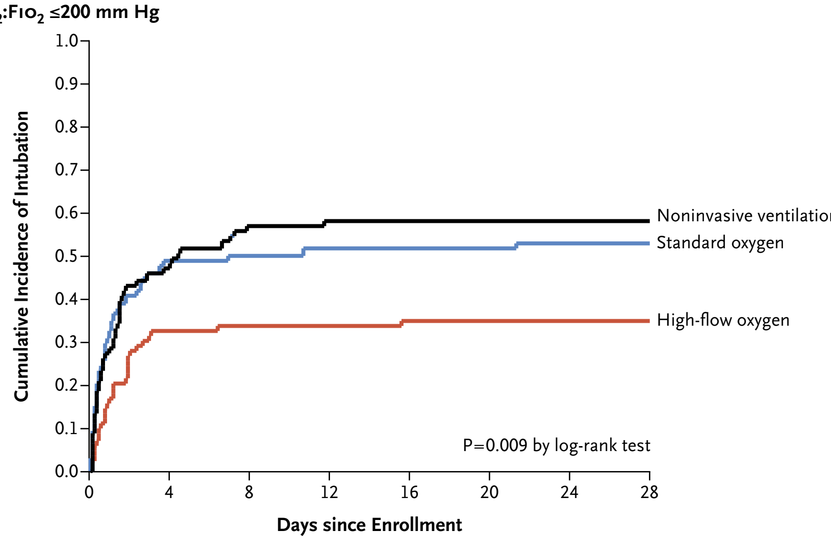
A Overall Population



No. at Risk

High-flow oxygen	106	68	67	67	65	65	65	65
Standard oxygen	94	52	50	49	49	49	48	48
Noninvasive ventilation	110	64	57	53	53	53	53	52

B Patients with a Pa_{O_2}:F_{IO_2} ≤200 mm Hg



No. at Risk

High-flow oxygen	83	55	54	54	53	53	53	53
Standard oxygen	74	37	35	34	34	34	33	33
Noninvasive ventilation	81	41	34	32	32	32	32	32

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 Pa_{O_2}:F_{IO_2} of 200 mm Hg or less are shown. Pa_{O_2}:F_{IO_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 Pa_{O_2}:F_{IO_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 Pa_{O_2}:F_{IO_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 Pa_{O_2}:F_{IO_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 Pa_{O_2}:F_{IO_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 Pa_{O_2}:F_{IO_2} ≤200 mm Hg	24±8	21±10	18±12	<0.001	—	—

Table 2. (Continued.)

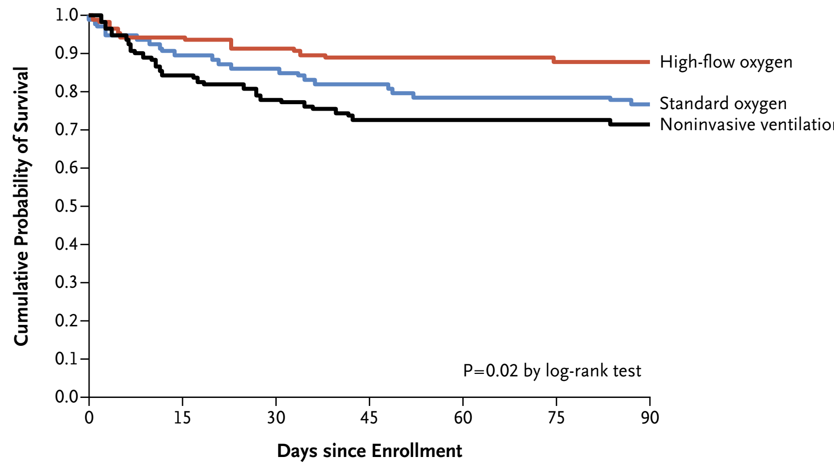
Outcome	Study Group			P Value†	Odds Ratio or Hazard Ratio (95% CI)	
	High-Flow Oxygen (N=106)	Standard Oxygen (N=94)	Noninvasive Ventilation (N=110)		Standard Oxygen vs. High-Flow Oxygen	Noninvasive Ventilation vs. High-Flow Oxygen
Death						
In ICU						
Unadjusted analysis				0.047	1.85 (0.84–4.09)	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 Pa_{O_2}:FI_{O_2} with respect to status regarding intubation was significant (P=0.01) in the subgroup of patients with a Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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 Pa_{O_2}:FI_{O_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 (Pa_{O_2}:F_{IO_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 Pa_{O_2}:F_{IO_2} of 200 mm Hg or less, which was justified by a significant interaction between Pa_{O_2}:F_{IO_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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Critique of:

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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

Objective

To determine whether high-flow nasal cannula oxygen therapy reduces the need for intubation in patients with acute hypoxemic respiratory failure without hypercapnia.

Design

Prospective, randomized, multicenter, open-label 3-arm trial.

Setting

Twenty-three intensive care units in France and Belgium.

Subjects

A total of 310 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 (P/F ratio) of 300 mm Hg or less on face mask oxygen. Patients with hypercarbia, chronic respiratory failure, obstructive lung disease or congestive heart failure exacerbation or acute indication for intubation were excluded.

Intervention

High-flow oxygen therapy using the OptiFlow device, standard oxygen therapy delivered through a face mask, or noninvasive positive-pressure ventilation.

Outcomes

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

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.

Abstract adapted from the original provided courtesy of PubMed: A service of the National Library of Medicine and the National Institutes of Health.

Commentary

Acute respiratory failure (ARF) accounts for one-third of intensive care unit (ICU) admission, resulting in a twofold increase in ICU mortality and prolonged ICU length of stay[2,3]. ARF requiring endotracheal intubation and mechanical ventilation brings increased risk of mortality and morbidity, yet the optimal time to initiate ventilator support remains unclear. Noninvasive positive-pressure ventilation (NIPPV) reduces the risk of intubation and mortality in patients with hypercarbic ARF from exacerbation of obstructive lung disease[4] and in patients with cardiogenic pulmonary edema[4,5]. NIPPV has not shown consistent benefits in patients with hypoxemic ARF from pneumonia or acute respiratory distress syndrome (ARDS), with some suggestion of worsened outcomes with "de novo" pneumonia[6,7]. NIPPV may prevent secretion clearance and is not advisable on patients unable to remove the mask due to aspiration risk[6,7]. In such patients, alternative means of non-invasive respiratory support may be desirable.

High-flow nasal cannula (HFNC) oxygen devices deliver up to 40–60L/min at a precise fraction of inspired oxygen (F_iO_2). High flow rates match the patient's peak inspiratory flow to prevent room air entrainment and improve comfort, while heat and humidification may prevent airway desiccation to improve mucociliary clearance[8]. By flushing carbon dioxide from the airways, HFNC reduces anatomic dead space to increase ventilatory efficiency and reduce work of breathing, in addition to producing minimal levels of positive end-expiratory pressure[8].

The FLORALI study randomized 310 patients with hypoxemic ARF to nonrebreather face mask, HFNC using the OptiFlow device (Fisher and Paykel Healthcare) or NIPPV with inspiratory pressure titrated to achieve tidal volume 7–10cc/kg[1]. The majority of patients had pneumonia and met criteria for ARDS, with bilateral infiltrates and a ratio of P_aO_2 to F_iO_2 (P/F ratio) <=200 on face mask oxygen. The study excluded patients likely to benefit from NIPPV, including those with hypercarbia, exacerbations of obstructive lung disease or cardiogenic pulmonary edema, along with patients likely to be harmed by NIPPV, including those with hemodynamic instability or depressed mental status. There was no significant reduction in the rate of intubation between groups in the main study population (p = 0.18). A *post hoc* subgroup analysis in patients with a PF ratio <=200 showed a significantly higher risk of intubation with face-mask oxygen (HR 2.07) or NIPPV (HR 2.57) compared to HFNC (p = 0.009). HFNC was associated with lower mortality in the ICU (p = 0.047) and at 90 days (p = 0.02) in both unadjusted and adjusted analyses, with HR's ranging from 1.85 to 2.60. Patients in the HFNC group had more ventilator-free days and lower dyspnea scores.

Strengths of this study include multi-center, randomized, intention-to-treat design with enrollment from 23 large ICU's[9]. Patients expected to benefit from NIPPV were systematically excluded. Since rate of intubation was the primary endpoint, a protocol was used to standardize indications for intubation. Study groups were well-matched at baseline and follow-up was complete. The study has a number of limitations that must be considered when applying the results. This was a highly-selected population enriched in patients with ARDS due to pneumonia without obstructive lung disease or heart failure; only 21% of screened patients with hypoxemic ARF were eligible and 12.5% were included. Patients had limited extrapulmonary organ failure, which is a risk factor for HFNC failure in ARDS[10]. The study had limited statistical power for the primary endpoint, with an observed intubation rate of 45% compared to an anticipated intubation rate of 60%. Because the study failed to meet its prespecified primary endpoint, the significant results of the *post hoc* subgroup analysis and the secondary mortality endpoints are hypothesis-generating rather than conclusive. One-fourth of patients in the face mask arm and one-eighth of patients in the HFNC arm crossed over to receive NIPPV; approximately two-thirds of these patients required intubation. It remains unclear why fewer people died in the HFNC arm, although the 7–10cc/kg tidal volume in the NIPPV arm exceeds the recommended 6cc/kg that has been associated with lower mortality in patients with ARDS[11,12]. Protocolized intubation criteria may have delayed intubation, as reflected by the occurrence of two deaths during intubation. While the study's protocolized intubation criteria seem reasonable as part of a research study, the decision to intubate requires considerable judgment and is difficult to fit to a protocol.

The FLORALI study emphasizes that the approach noninvasive respiratory support in ARF should be tailored to both the underlying physiology (hypoxemic versus hypercarbic ARF) and the causative disease process. HFNC may become the preferred noninvasive modality for patients with hypoxemic ARF due to pneumonia or ARDS, while NIPPV will remain preferred for patients with obstructive lung disease or cardiogenic pulmonary edema. Other recent studies of HFNC have shown mixed results depending on the population studied. HFNC failed to show a benefit over NIPPV for pre-oxygenation prior to intubation, although HFNC during intubation did reduce the risk of desaturation during intubation when compared to face mask[13,14]. HFNC was inferior to NIPPV for respiratory support during bronchoscopy[15]. HFNC performed equally compared to NIPPV for patients developing ARF after cardiothoracic surgery[16]. Further studies are needed to guide our use of HFNC for patients with ARF, and several ongoing studies of HFNC are listed on clinicaltrials.gov.

Recommendation

HFNC is safe and can be considered for first line support of patients with severe hypoxemic ARF not requiring immediate intubation, including pneumonia and early ARDS in the absence of hypercarbia, obstructive lung disease or heart failure exacerbation. Careful monitoring in an ICU during HFNC is essential to ensure timely escalation of therapy in the event of HFNC failure. With either HFNC or NIPPV, intubation should be performed before the patient exhausts their physiologic reserves and decompensates.

Competing interests

The authors declare that they have no competing interests.

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