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# Effect of Postextubation High-Flow Nasal Oxygen With Noninvasive Ventilation vs High-Flow Nasal Oxygen Alone on Reintubation Among Patients at High Risk of Extubation Failure: A Randomized Clinical Trial

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**IMPORTANCE** High-flow nasal oxygen may prevent postextubation respiratory failure in the intensive care unit (ICU). The combination of high-flow nasal oxygen with noninvasive ventilation (NIV) may be an optimal strategy of ventilation to avoid reintubation.

**OBJECTIVE** To determine whether high-flow nasal oxygen with prophylactic NIV applied immediately after extubation could reduce the rate of reintubation, compared with high-flow nasal oxygen alone, in patients at high risk of extubation failure in the ICU.

**DESIGN, SETTING, AND PARTICIPANTS** Multicenter randomized clinical trial conducted from April 2017 to January 2018 among 641 patients at high risk of extubation failure (ie, older than 65 years or with an underlying cardiac or respiratory disease) at 30 ICUs in France; follow-up was until April 2018.

**INTERVENTIONS** Patients were randomly assigned to high-flow nasal oxygen alone (n = 306) or high-flow nasal oxygen with NIV (n = 342) immediately after extubation.

**MAIN OUTCOMES AND MEASURES** The primary outcome was the proportion of patients reintubated at day 7; secondary outcomes included postextubation respiratory failure at day 7, reintubation rates up until ICU discharge, and ICU mortality.

**RESULTS** Among 648 patients who were randomized (mean [SD] age, 70 [10] years; 219 women [34%]), 641 patients completed the trial. The reintubation rate at day 7 was 11.8% (95% CI, 8.4%-15.2%) (40/339) with high-flow nasal oxygen and NIV and 18.2% (95% CI, 13.9%-22.6%) (55/302) with high-flow nasal oxygen alone (difference, -6.4% [95% CI, -12.0% to -0.9%];  $P = .02$ ). Among the 11 prespecified secondary outcomes, 6 showed no significant difference. The proportion of patients with postextubation respiratory failure at day 7 (21% vs 29%; difference, -8.7% [95% CI, -15.2% to -1.8%];  $P = .01$ ) and reintubation rates up until ICU discharge (12% vs 20%, difference -7.4% [95% CI, -13.2% to -1.8%];  $P = .009$ ) were significantly lower with high-flow nasal oxygen and NIV than with high-flow nasal oxygen alone. ICU mortality rates were not significantly different: 6% with high-flow nasal oxygen and NIV and 9% with high-flow nasal oxygen alone (difference, -2.4% [95% CI, -6.7% to 1.7%];  $P = .25$ ).

**CONCLUSIONS AND RELEVANCE** In mechanically ventilated patients at high risk of extubation failure, the use of high-flow nasal oxygen with NIV immediately after extubation significantly decreased the risk of reintubation compared with high-flow nasal oxygen alone.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: [NCT03121482](https://clinicaltrials.gov/ct2/show/study/NCT03121482)

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In intensive care units (ICUs), approximately 10% to 15% of patients ready to be separated from a ventilator experience extubation failure leading to reintubation.<sup>1</sup> In patients considered at high risk, these rates can even exceed 20%.<sup>1,2</sup> Because reintubation is associated with particularly high mortality,<sup>3,4</sup> a strategy of oxygenation aimed at avoiding reintubation deserves consideration. Although noninvasive ventilation may prevent postextubation respiratory failure in patients at high risk,<sup>5-9</sup> only 2 small-scale randomized clinical trials (RCTs) have shown decreased reintubation rates compared with standard oxygen.<sup>5,6</sup> The most recent international clinical practice guidelines recommend the use of noninvasive ventilation to prevent postextubation respiratory failure in patients at high risk of extubation failure.<sup>10</sup> However, up until now, no large-scale RCT has demonstrated a significant reduction of reintubation rates with noninvasive ventilation compared with standard oxygen. Thereby, most patients are treated with standard oxygen in clinical practice and only 10% of them receive noninvasive ventilation after extubation in the ICU.<sup>2,11</sup>

High-flow nasal oxygen is an alternative strategy that may reduce the risk of reintubation in the ICU compared with standard oxygen.<sup>12,13</sup> A large-scale RCT has reported that high-flow nasal oxygen was noninferior to noninvasive ventilation in preventing reintubation in patients at high risk.<sup>14</sup> Whereas high-flow nasal oxygen could be considered as a reference treatment after extubation, using high-flow nasal oxygen with noninvasive ventilation may further improve gas exchange and the work of breathing,<sup>15</sup> thereby avoiding reintubation.

This multicenter RCT involving patients at high risk of extubation failure in the ICU was conducted to determine whether high-flow nasal oxygen with noninvasive ventilation, compared with high-flow nasal oxygen alone, after extubation could reduce the rate of reintubation.

## Methods

The study was conducted in 30 ICUs in France. For all the centers, the study protocol (Supplement 1) was approved by the central ethics committee (Ethics Committee Ouest III, Poitiers, France; registration No. 2016-A01078-43). Written informed consent was obtained from all patients or next of kin before inclusion in the study.

Adult patients intubated more than 24 hours in the ICU and ready for extubation, after a successful spontaneous breathing trial performed according to the international conference consensus on weaning,<sup>16</sup> were enrolled if they were at high risk of extubation failure (ie, older than 65 years or had any underlying chronic cardiac or lung disease).<sup>10</sup> Underlying chronic cardiac diseases included left ventricular dysfunction, whatever the cause, defined by left ventricular ejection fraction equal to or below 45%; history of cardiogenic pulmonary edema; documented ischemic heart disease; or permanent atrial fibrillation. Underlying chronic lung diseases included chronic obstructive pulmonary disease, obesity-hypoventilation syndrome, or restrictive pulmonary disease.

The main exclusion criteria were long-term treatment with noninvasive ventilation or continuous positive airway pres-

## Key Points

**Question** Among mechanically ventilated patients at high risk of extubation failure, does the use of high-flow nasal oxygen with noninvasive ventilation after extubation reduce the risk of reintubation compared with high-flow nasal oxygen alone?

**Findings** In this randomized clinical trial that included 641 patients, high-flow nasal oxygen with noninvasive ventilation, compared with high-flow nasal oxygen alone, significantly decreased the rate of reintubation within the first 7 days after extubation (11.8% vs 18.2%).

**Meaning** In patients at high risk of extubation failure, the use of high-flow nasal oxygen with noninvasive ventilation after extubation significantly decreased the risk of reintubation compared with high-flow nasal oxygen alone.

sure at home, contraindication to noninvasive ventilation, underlying chronic neuromuscular disease (myopathy or myasthenia gravis), or traumatic brain injury leading to intubation, as well as patients who underwent unplanned extubation (accidental or self-extubation) or with a do-not-reintubate order at time of extubation.

The trial was overseen by a steering committee that presented information regarding the progression and monitoring of the study at REVA (Réseau Européen de Recherche en Ventilation Artificielle) Network meetings every 6 months. No safety committee was required because the interventions used in the study were strategies of oxygenation typically used in clinical practice. 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 daily patient screening, 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 January 2019.

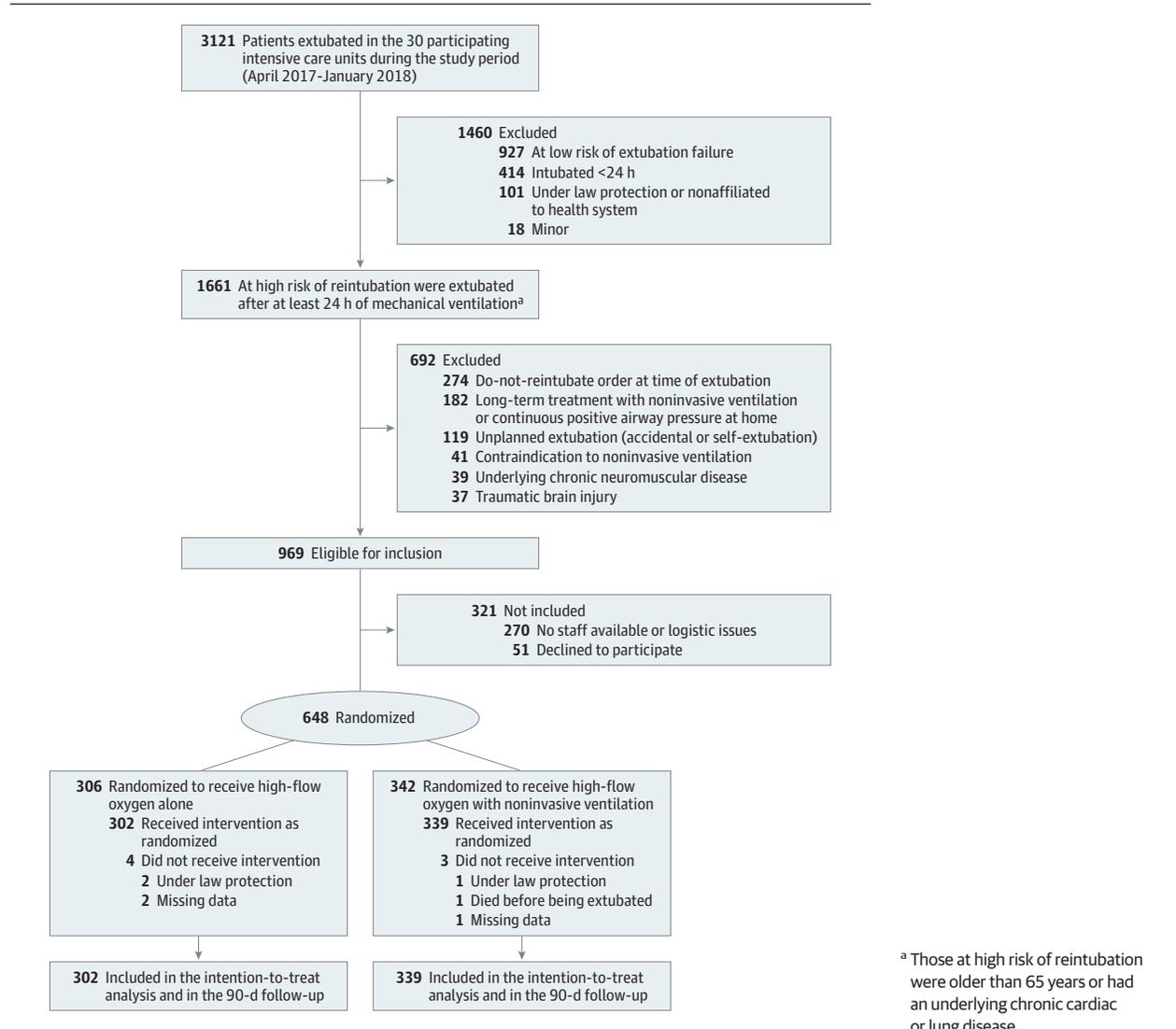
## Randomization

Randomization was computer-generated using a centralized web-based management system in permuted blocks of 4 participants (unknown to investigators), with stratification according to the center and arterial partial pressure of carbon dioxide (Paco<sub>2</sub>) level ( $\leq 45$  or  $>45$  mm Hg) measured at the end of the spontaneous breathing trial (or under mechanical ventilation before the trial if this latter was not measured). Stratification was performed on Paco<sub>2</sub> level to include the same number of hypercapnic patients in the 2 groups because noninvasive ventilation may be more effective in these patients.<sup>7,8</sup> Patients were randomly assigned in a 1:1 ratio to receive high-flow nasal oxygen alone (control group) or with noninvasive ventilation (intervention group) immediately after extubation (Figure 1).

## Interventions

Patients assigned to the control group were continuously treated by high-flow nasal oxygen alone for at least 48 hours

Figure 1. Flow of Patients in the HIGH-Wean Trial of High-Flow Nasal Oxygen With or Without Noninvasive Ventilation



with a flow of 50 L/min and fraction of inspired oxygen (FIO<sub>2</sub>) adjusted to obtain adequate oxygenation, with an oxygen saturation as measured by pulse oximetry (SpO<sub>2</sub>) of at least 92%. To provide sufficient humidification, the temperature of the heated humidifier was set at 37°C as during invasive mechanical ventilation.

Patients assigned to the intervention group (referred to here as the noninvasive ventilation group) were treated with high-flow nasal oxygen with noninvasive ventilation. Noninvasive ventilation was initiated immediately after extubation with a first session of at least 4 hours and minimal duration of at least 12 hours a day during the 48 hours following extubation. Continuous application of noninvasive ventilation was promoted throughout the entire night period. Noninvasive ventilation was carried out with an ICU ventilator with noninvasive ventilation mode or dedicated bilevel ventilator in pressure-support mode with a minimal pressure-support level of 5 cm H<sub>2</sub>O targeting a tidal volume around 6 to 8 mL/kg of

predicted body weight, a positive end-expiratory pressure level between 5 and 10 cm H<sub>2</sub>O, and a FIO<sub>2</sub> adjusted to obtain adequate oxygenation (SpO<sub>2</sub> ≥92%). Between noninvasive ventilation sessions, high-flow nasal oxygen was delivered as in the control group. Blood gases were performed 1 hour after treatment initiation under high-flow oxygen in the high-flow nasal oxygen alone group and under noninvasive ventilation in the noninvasive ventilation group. In the 2 groups, patients were treated for a minimum of 48 hours. When there were no signs of respiratory failure 48 hours after extubation, treatment was stopped and switched to standard oxygen. According to patient respiratory status, treatment could be continued until complete respiratory recovery. In case of established postextubation respiratory failure, the use of noninvasive ventilation was discouraged in accordance with the most recent international clinical practice guidelines,<sup>10</sup> given that it has no proven benefit<sup>17</sup> and can even increase the risk of death by delaying reintubation.<sup>18</sup>

## Outcomes

The primary outcome was the proportion of patients who required reintubation within the 7 days following extubation. To ensure the consistency of indications across sites and reduce the risk of delayed intubation, patients were immediately reintubated if 1 of the following criteria was fulfilled: severe respiratory failure, hemodynamic failure with the need for vasopressors, neurological failure (altered consciousness with a Glasgow Coma Scale score <12), or cardiac or respiratory arrest. Severe respiratory failure leading to reintubation was defined by the presence of at least 2 criteria among the following: a respiratory rate greater than 35 breaths per minute, clinical signs suggesting respiratory distress with activation of accessory respiratory muscles, respiratory acidosis defined as a pH level below 7.25 units and  $\text{PaCO}_2$  greater than 45 mm Hg, hypoxemia defined as a need for  $\text{FIO}_2$  at 80% or more to maintain an  $\text{SpO}_2$  level at 92% or more, or a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ( $\text{PaO}_2:\text{FIO}_2$ ) equal to or below 100 mm Hg.

Secondary outcomes included reintubation at 48 hours, 72 hours, and up until ICU discharge; an episode of postextubation respiratory failure within 7 days following extubation; the proportion of patients in whom the treatment was continued beyond the first 48 hours following extubation; length of stay in the ICU and in the hospital; and mortality in the ICU, in the hospital, at day 28, and at day 90. An episode of postextubation respiratory failure was defined by the presence of at least 2 criteria among the following: a respiratory rate greater than 25 breaths per minute, clinical signs suggesting respiratory distress, respiratory acidosis defined as a pH level less than 7.35 units and  $\text{PaCO}_2$  level greater than 45 mm Hg, hypoxemia defined as a need for  $\text{FIO}_2$  at least 50% to maintain  $\text{SpO}_2$  level of at least 92%, or a  $\text{PaO}_2:\text{FIO}_2$  ratio equal to or below 150 mm Hg.

Exploratory outcomes included blood gases 1 hour after treatment initiation, time to reintubation, the proportion of patients who met criteria for reintubation, reasons for reintubation, use of noninvasive ventilation as rescue therapy, the proportion of patients who were reintubated or died in the ICU, and mortality of reintubated patients.

## Statistical Analysis

Enrollment of 590 patients was determined to provide a power of 80% and to show an absolute difference of 8% in the rate of reintubation between the control group using high-flow nasal oxygen alone (rate of reintubation estimated to 18%) compared with the intervention group using high-flow nasal oxygen and noninvasive ventilation (rate of reintubation estimated to 10%) at a 2-sided  $\alpha$  level of .05 (ie, exactly the same difference as that planned in a previous RCT comparing high-flow nasal oxygen vs standard oxygen on reintubation among patients at low risk of extubation failure<sup>13</sup>). To allow for the potential secondary exclusions, the number of patients to be enrolled was then inflated to 650 patients (increased by 10%).

All the analyses were performed by the study statistician according to a predefined statistical analysis plan. The analy-

sis was performed on all randomized patients who were extubated and for whom the primary outcome was completed. Patients were analyzed according to their randomization group regardless of the treatment applied. The proportions of patients having needed reintubation within the 7 days following planned extubation were compared between the 2 groups by means of the  $\chi^2$  test.

Kaplan-Meier curves were plotted to assess time from extubation to reintubation and were compared by means of the log-rank test at day 7. Reintubation rates at the various predefined times, postextubation respiratory failure rates at day 7, and mortality rates in the ICU and hospital were compared between the 2 groups by means of the  $\chi^2$  test. Kaplan-Meier curves were plotted to assess the time from extubation to death and were compared by means of the log-rank test at day 90.

A multiple logistic regression analysis was performed for the primary outcome to adjust on the stratification variable ( $\text{PaCO}_2$  level) and on potential baseline unbalanced variables. Lack of balance was defined as  $P < .05$ , and the only variable ultimately included in the model was underlying chronic lung disease. The results were presented as odds ratios with 95% CIs. A post hoc random-effects multilevel logistic regression model was used to take into account the effect of the hospital. Treatment group was introduced in the model as a fixed effect and hospital was introduced in the model as a random effect. A subgroup analysis was performed for the primary and secondary outcomes according to the  $\text{PaCO}_2$  level ( $\leq 45$  or  $> 45$  mm Hg) prior to extubation after an interaction test carried out to detect heterogeneity of treatment effect between hypercapnic and nonhypercapnic patients. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. A 2-tailed  $P$  value of less than .05 was considered to indicate statistical significance. We used SAS software version 9.4 (SAS Institute) for all analyses.

## Results

### Study Participants

From April 2017 through January 2018, 3121 patients were extubated in the 30 participating units, 969 were eligible for inclusion in the study, and 648 underwent randomization (mean [SD] age, 70 [10] years; 219 women [34%]) (Figure 1). Seven patients were secondarily excluded because they were protected under French law, which was not known at randomization ( $n = 3$ ), died before extubation ( $n = 1$ ), or were missing data for the primary outcome ( $n = 3$ ), leaving 641 patients included in the analysis: 302 patients were assigned to high-flow nasal oxygen alone and 339 to high-flow nasal oxygen with non-invasive ventilation.

The characteristics of the patients at inclusion were similar in the 2 groups except for a higher proportion of patients with underlying chronic lung disease in the noninvasive ventilation group (Table 1). The median duration of mechanical ventilation prior to extubation was 5 days (interquartile range [IQR], 3-10), and weaning was considered

Table 1. Baseline Patient Characteristics<sup>a</sup>

Characteristic	No. (%)	
	High-Flow Nasal Oxygen Alone (n = 302)	High-Flow Nasal Oxygen With NIV (n = 339)
Characteristics of the patients at admission		
Age, mean (SD), y	70 (10)	69 (10)
Sex		
Men	195 (65)	230 (68)
Women	107 (35)	109 (32)
Body mass index, mean (SD) <sup>b</sup>	28 (6)	28 (7)
SAPS II score at admission, mean (SD) <sup>c</sup>	55 (17)	55 (20)
Main reason for intubation		
Acute respiratory failure	158 (52)	167 (49)
Coma	55 (18)	57 (17)
Shock	30 (10)	37 (11)
Cardiac arrest	26 (9)	35 (10)
Surgery	28 (9)	35 (10)
Other reason	5 (2)	8 (2)
Risk factors of extubation failure		
Age >65 y	223 (74)	237 (70)
Underlying chronic cardiac disease <sup>d</sup>	145 (48)	161 (47)
Ischemic heart disease	78 (26)	88 (26)
Atrial fibrillation	58 (19)	45 (13)
Left ventricular dysfunction	39 (13)	52 (15)
History of cardiogenic pulmonary edema	21 (7)	25 (7)
Underlying chronic lung disease <sup>d</sup>	87 (29)	126 (37)
Chronic obstructive pulmonary disease	64 (21)	86 (25)
Obesity-hypoventilation syndrome	16 (5)	20 (6)
Chronic restrictive pulmonary disease	12 (4)	24 (7)
Characteristics of the patients the day of extubation		
SOFA score, mean (SD) <sup>e</sup>	4.2 (2.5)	4.4 (2.7)
Duration of mechanical ventilation, median (IQR), d	5 (3-9)	6 (3-11)
Weaning difficulty <sup>f</sup>		
Simple	203 (67)	232 (68)
Difficult	92 (31)	93 (27)
Prolonged	7 (2)	14 (4)
Ventilator settings before the spontaneous breathing trial		
Assist-control ventilation	42 (14)	49 (14)
Pressure-support ventilation	260 (86)	290 (86)
Pressure-support level, mean (SD), cm H <sub>2</sub> O	9.6 (2.8)	9.3 (2.9)
Positive end-expiratory pressure, mean (SD), cm H <sub>2</sub> O	5.7 (1.6)	5.9 (1.6)
Tidal volume, mean (SD)		
mL	468 (125)	479 (144)
mL/kg	7.7 (2.4)	7.9 (2.5)
Respiratory rate, mean (SD), breaths/min	22 (7)	22 (6)
F <sub>IO<sub>2</sub></sub> , mean (SD), %	35 (10)	35 (11)
Median (IQR)	30 (30-40)	30 (30-40)
PaO <sub>2</sub> :F <sub>IO<sub>2</sub></sub> , mean (SD), mm Hg	274 (93)	275 (89)
pH, mean (SD), units	7.45 (0.06)	7.45 (0.05)
Paco <sub>2</sub> mean (SD), mm Hg	40 (8)	40 (8)

(continued)

Table 1. Baseline Patient Characteristics<sup>a</sup> (continued)

Characteristic	No. (%)	
	High-Flow Nasal Oxygen Alone (n = 302)	High-Flow Nasal Oxygen With NIV (n = 339)
Characteristics at the end of the spontaneous breathing trial		
T-piece trial	188 (62)	206 (61)
Low level of pressure support	114 (38)	133 (39)
Duration of the trial, median (IQR), min	60 (30-60)	60 (30-60)
Arterial pressure, mean (SD), mm Hg		
Systolic	136 (21)	136 (22)
Diastolic	67 (14)	68 (16)
Heart rate, mean (SD), bpm	92 (17)	92 (18)
Respiratory rate, mean (SD), breaths/min	23 (6)	23 (6)
SpO <sub>2</sub> , mean (SD), %	96 (3)	96 (3)
PaO <sub>2</sub> , mm Hg		
Mean (SD) [No.]	87 (28) [221]	86 (27) [241]
pH, units		
Mean (SD) [No.]	7.45 (0.06) [221]	7.45 (0.05) [241]
Paco <sub>2</sub> , mm Hg		
Mean (SD) [No.]	39 (8) [221]	40 (9) [241]
Administration of steroids before extubation		
Ineffective cough, No./No. (%)	65/284 (23)	86/322 (27)
Abundant secretions, No./No. (%)	121/288 (42)	114/326 (35)
Participating centers (n = 30)		
No. of centers that participated	30 (100)	30 (100)
No. of patients per center, median (IQR)	10 (9-25)	13 (9-23)
Abbreviations: bpm, beats per minute; FIO <sub>2</sub> , fraction of inspired oxygen; IQR, interquartile range; NIV, noninvasive ventilation; Paco <sub>2</sub> , arterial partial pressure of carbon dioxide; PaO <sub>2</sub> , partial pressure of arterial oxygen; SAPS, Simplified Acute Physiology Score; SOFA, Sequential (Sepsis-Related) Organ Failure Assessment; SpO <sub>2</sub> , oxygen saturation as measured by pulse oximetry.		
<sup>a</sup> The only significant differences in baseline characteristics between the 2 trial groups were the proportion of patients with underlying chronic lung disease (P = .02).		
<sup>b</sup> Calculated as weight in kilograms divided by height in meters squared.		
<sup>c</sup> The SAPS II score was calculated from 17 variables at admission. Scores range from 0 to 163, with higher scores indicating more severe disease and higher mortality risk. Patients with a SAPS II score of 55 at admission have a predicted mean 43% chance of survival.		
<sup>d</sup> Patients could have more than 1 underlying chronic cardiac or lung disease.		
<sup>e</sup> The SOFA score was calculated from 6 variables the day of extubation. Scores range from 0 to 24, with higher scores indicating more severe organ failure and higher mortality risk. Patients with a SOFA score between 4 and 5 have a predicted mean chance of survival >90%.		
<sup>f</sup> Weaning difficulty was defined as follows: simple weaning included patients extubated after success of the first spontaneous breathing trial, difficult weaning included patients who failed the first spontaneous breathing trial and were extubated within the 7 following days, and prolonged weaning included patients extubated more than 7 days after the first spontaneous breathing trial.		

difficult or prolonged in 32% of patients (206 of 641 patients). At the time of extubation, 111 patients (17%) had hypercapnia (Paco<sub>2</sub> >45 mm Hg).

Initial mean (SD) settings were as follows: in the high-flow nasal oxygen alone group, the gas flow rate was 50 (5) L/min with FIO<sub>2</sub> of 0.41 (0.13); in the noninvasive ventilation group, the pressure-support level was 7.8 (2.5) cm H<sub>2</sub>O, PEEP was 5.3 (1.1) cm H<sub>2</sub>O, and FIO<sub>2</sub> was 0.34 (0.10), resulting in a tidal volume of 8.6 (2.9) mL/kg of predicted body weight.

In the noninvasive ventilation group, noninvasive ventilation was delivered for a mean (SD) of 22 (9) hours within the first 48 hours following extubation (mean of 13 hours within the first 24 hours) and was delivered for 4 hours or less due to intolerance in 20 patients (6%). In the high-flow nasal oxygen alone group, high flow nasal oxygen was delivered for a mean (SD) of 42 (11) hours within the first 48 hours.

### Primary Outcome

The reintubation rate at day 7 was 11.8% (95% CI, 8.4%-15.2%) with noninvasive ventilation and 18.2% (95% CI, 13.9%-22.6%) with high-flow nasal oxygen alone (difference, -6.4% [95% CI, -12.0 to -0.9]; P = .02) (Figure 2).

### Secondary Outcomes

Reintubation rates were also significantly lower with noninvasive ventilation than with high-flow nasal oxygen alone at 48 hours, 72 hours, and until ICU discharge (Table 2). The proportion of patients with postextubation respiratory failure at day 7 was significantly lower with noninvasive ventilation than with high-flow nasal oxygen alone (21% vs 29%; difference, -8.7% [95% CI, -15.2% to -1.8%]; P = .01). In the noninvasive ventilation group, noninvasive ventilation was continued beyond the first 48 hours for incomplete recovery of respiratory

status in 86 patients (25%), whereas in the high-flow nasal oxygen alone group, high-flow nasal oxygen was continued in 106 patients (35%) (difference,  $-9.7\%$  [95% CI,  $-16.8\%$  to  $-2.6\%$ ];  $P < .01$ ). Mortality in the ICU, in the hospital, and at day 90 were not significantly different between groups (Table 2; eFigure in Supplement 2).

### Exploratory Outcomes

One hour after treatment initiation,  $\text{PaO}_2:\text{FiO}_2$  was higher with noninvasive ventilation than with high-flow nasal oxygen alone (mean [SD], 291 [97] mm Hg vs 254 [113] mm Hg; difference, 37.0 [95% CI, 19.7 to 54.3];  $P < .001$ ), whereas the proportion of patients with hypercapnia did not differ (21% vs 19%, respectively; difference, 1.2% [95% CI,  $-5.4\%$  to  $7.7\%$ ];  $P = .72$ ).

The median time to reintubation was not significantly different between groups: 33 hours (IQR, 7-81) with noninvasive ventilation and 39 hours (IQR, 12-67) with high-flow nasal oxygen alone (difference,  $-5.0$  [95% CI,  $-42.0$  to  $32.0$ ];  $P = .76$ ).

Among the 100 patients who were reintubated in the ICU, 96% met prespecified criteria for reintubation: 95% (39/41) in the noninvasive ventilation group vs 97% (57/59) in the high-flow nasal oxygen alone group (difference,  $-1.5\%$  [95% CI,  $-13.0\%$  to  $7.4\%$ ];  $P = .99$ ). The reason for reintubation was severe respiratory failure in 88 patients, neurological failure in 37 patients, hemodynamic failure in 16 patients, and respiratory or cardiac arrest in 10 patients (eTable 1 in Supplement 2).

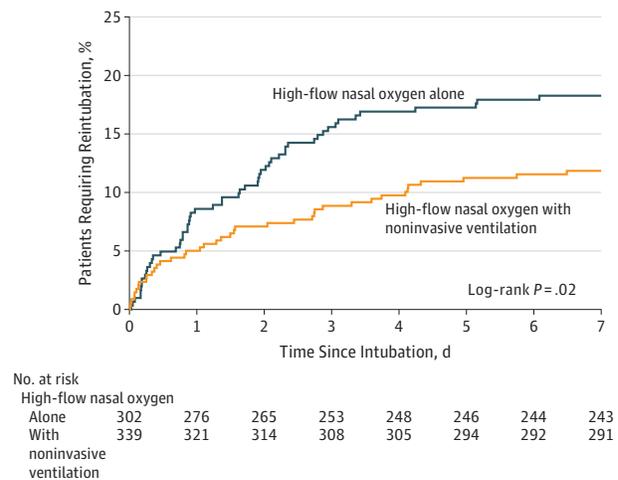
Among the 70 patients who had postextubation respiratory failure with high-flow nasal oxygen alone, 20 patients (29%) were treated with noninvasive ventilation as rescue therapy delivered for a mean (SD) of 7 (6) hours, of which 10 patients (50%) needed reintubation. Results for additional exploratory outcomes are shown in Table 2.

### Subgroup Analysis and Additional Analyses

No significant interaction was noted between  $\text{PaCO}_2$  at enrollment and treatment group with respect to the primary outcome ( $P$  for interaction = .25). Among the 111 patients with  $\text{PaCO}_2$  greater than 45 mm Hg before extubation, the reintubation rate at day 7 was significantly lower with noninvasive ventilation than with high-flow nasal oxygen alone (8% vs 21%; difference,  $-12.9\%$  [95% CI,  $-27.1\%$  to  $-0.1\%$ ];  $P = .049$ ) (Figure 3). Among the 530 patients with  $\text{PaCO}_2$  of 45 mm Hg or less, reintubation rates at day 7 were not significantly different between groups (13% with noninvasive ventilation vs 18% with high-flow nasal oxygen alone; difference,  $-5.0\%$  [95% CI,  $-11.2\%$  to  $1.1\%$ ];  $P = .10$ ) (eTables 2, 3, and 4 in Supplement 2).

After adjustment for  $\text{PaCO}_2$  level at enrollment ( $\leq 45$  or  $> 45$  mm Hg, stratification randomization variable) and underlying chronic lung disease (variable unbalanced between both groups indicated in Table 1), the odds ratio for reintubation at day 7 was significantly lower with noninvasive ventilation than with high-flow nasal oxygen alone (adjusted odds ratio, 0.60 [95% CI, 0.38-0.93];  $P = .02$ ). The post hoc analysis showed a lower reintubation rate with noninvasive ventilation than with high-flow nasal oxygen alone after adjustment for the hospital random effect ( $P = .02$  without hospital random effect, and  $P = .02$  after adjustment for the hospital random effect) (eTable 5 in Supplement 2).

Figure 2. Kaplan-Meier Analysis of Time From Extubation to Reintubation for the Overall Study Population



The median observation time was 7 days (interquartile range, 7-7) in both treatment groups.

During the study, there were no severe adverse events attributable to the randomization group.

## Discussion

In this multicenter, randomized, open-label trial, high-flow nasal oxygen with noninvasive ventilation, compared with high-flow nasal oxygen alone, decreased the rate of reintubation within the first 7 days after extubation in the ICU.

This study was designed to assess noninvasive ventilation in a large population of patients who are particularly easy to identify and extubated daily in the different ICUs. Although noninvasive ventilation may be beneficial on outcomes of hypercapnic patients,<sup>7,8</sup> these patients account for only about 20% to 30% of patients at high risk of extubation failure in the ICU.<sup>7,19</sup> Patients older than 65 years or with underlying chronic cardiac or respiratory disease are also at high risk of reintubation<sup>20</sup> and could benefit from noninvasive ventilation.<sup>21</sup>

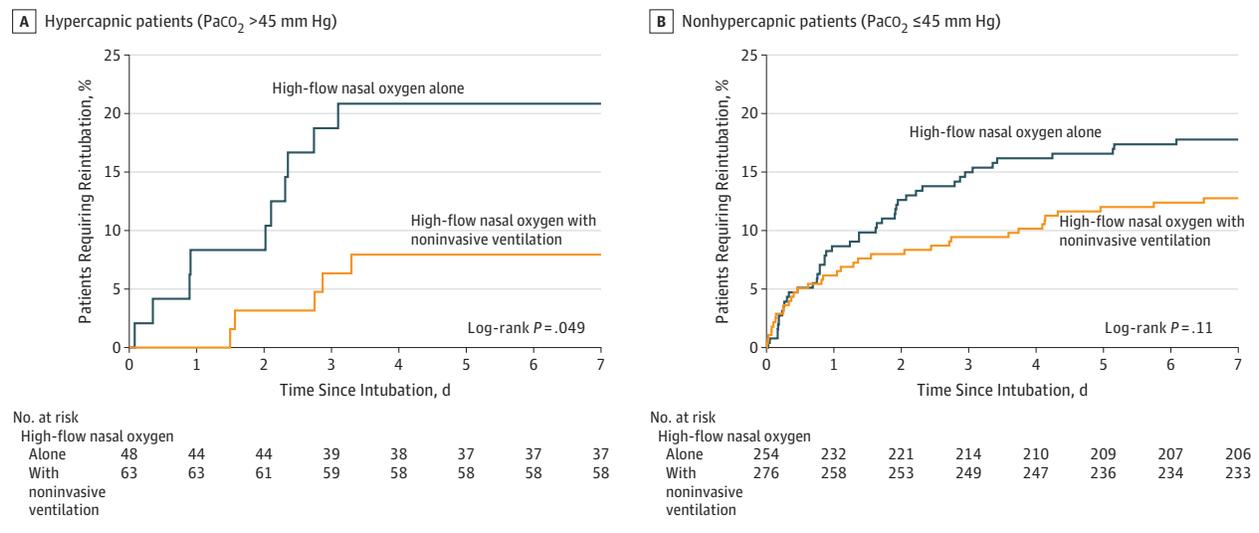
To our knowledge, the combination of high-flow nasal oxygen with noninvasive ventilation had not been previously assessed after extubation in the ICU. A preliminary study observed a reintubation rate of 15% at day 7 with noninvasive ventilation and standard oxygen in exactly the same population.<sup>21</sup> Therefore, the study hypothesized that a new strategy combining high-flow nasal oxygen with noninvasive ventilation could further reduce the rate of reintubation, whereas the estimated rate would exceed 15% in the control group.<sup>13,14</sup> For an overall reintubation rate around 15% in the ICU,<sup>22</sup> an absolute difference of at least 5% (relative reduction of one-third) would be considered clinically significant and in the range of previous large multicenter RCTs assessing reintubation as the main outcome.<sup>13,23</sup> Reintubation rates were

Table 2. Primary, Secondary, and Exploratory Outcomes

	No. (%)		Absolute Difference, % (95% CI)	P Value
	High-Flow Nasal Oxygen Alone (n = 302)	High-Flow Nasal Oxygen With NIV (n = 339)		
<b>Primary Outcome</b>				
Reintubation at day 7	55 (18)	40 (12)	-6.4 (-12.0 to -0.9)	.02
<b>Secondary Outcomes</b>				
Reintubation				
Postextubation respiratory failure at day 7	88 (29)	70 (21)	-8.5 (-15.2 to -1.8)	.01
At 48 h	36 (12)	24 (7)	-4.8 (-9.6 to -0.3)	.04
At 72 h	47 (16)	30 (9)	-6.7 (-11.9 to -1.7)	.009
Up until ICU discharge	59 (20)	41 (12)	-7.4 (-13.2 to -1.8)	.009
Length of stay, median (IQR), days				
In ICU	11 (7 to 19)	12 (7 to 19)	0.5 (-1.6 to 2.6)	.55
In hospital	23 (15 to 39)	25 (15 to 42)	2.3 (-1.4 to 6.1)	.31
Mortality				
In ICU	26 (9)	21 (6)	-2.4 (-6.7 to 1.7)	.25
In hospital	46 (15)	54 (16)	0.7 (-5.0 to 6.3)	.80
At day 28	33 (11)	39 (12)	0.6 (-4.4 to 5.5)	.82
At day 90	65 (21)	62 (18)	-3.2 (-9.5 to 2.9)	.30
<b>Exploratory Outcomes</b>				
Patients meeting reintubation criteria during ICU stay	65 (22)	49 (14)	-7.1 (-13.1 to -1.1)	.02
Mortality or reintubation in ICU	64 (21)	51 (15)	-6.2 (-12.2 to -0.2)	.04
Mortality of reintubated patients	21/59 (36)	11/41 (27)	-8.8 (-25.7 to 9.9)	.35

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NIV, noninvasive ventilation.

Figure 3. Kaplan-Meier Analysis of Time From Extubation to Reintubation According to Predefined Strata



Results in hypercapnic patients with arterial partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) greater than 45 mm Hg (A) and in nonhypercapnic patients with  $\text{PaCO}_2$  of 45 mm Hg or less (B) are shown. The median observation time was 7 days (interquartile range, 7-7) in both treatment groups.

almost exactly the expected rates in the 2 groups (18.2% and 11.8%), reinforcing the external validity of the study.

To date, only 2 RCTs have observed lower reintubation rates with noninvasive ventilation than with standard oxygen.<sup>5,6</sup> To our knowledge, the present study is the largest RCT showing a reduced risk of reintubation after extubation in the ICU with noninvasive ventilation. Unlike a previous RCT

that reported similar reintubation rates between noninvasive ventilation and high-flow nasal oxygen applied 24 hours after extubation in nonhypercapnic patients,<sup>14</sup> this study combined noninvasive ventilation and high-flow nasal oxygen for at least 48 hours and treatment was prolonged if necessary. Although the beneficial effects of noninvasive ventilation on oxygenation, alveolar ventilation, and work of breathing are well

demonstrated,<sup>24,25</sup> continuation of high-flow nasal oxygen between sessions of noninvasive ventilation may further provide clinical improvement by decreasing work of breathing.<sup>15,26</sup>

Approximately one-third of patients treated with high-flow nasal oxygen alone received noninvasive ventilation as rescue therapy in case of postextubation respiratory failure. Although noninvasive ventilation as rescue therapy may avoid reintubation in a number of cases, it has been shown to possibly be deleterious and increase mortality in this setting.<sup>18</sup> Moreover, international clinical practice guidelines suggest that noninvasive ventilation should not be used in the treatment of patients with established postextubation respiratory failure.<sup>10</sup>

### Limitations

This study has several limitations. First, high-flow nasal oxygen rather than standard oxygen was used in the control group. However, it has been shown that reintubation rates with high-flow nasal oxygen were reduced as compared with standard oxygen.<sup>12,13</sup> According to clinical practice in participating centers, the use of standard oxygen alone would have been considered a suboptimal strategy for patients at high risk. Therefore, high-flow nasal oxygen was used in the control group to promote equipoise and facilitate inclusions in different centers.

Second, attending physicians could not be blinded to the study group and this could have modified the decision of reintubation by promoting early reintubation in patients treated with high-flow nasal oxygen alone. However, almost all reintubated patients met prespecified criteria for reintubation, and they had particularly high mortality (exceeding 30%), confirming high severity of patients who were reintubated.

Third, the weaning protocol and the type of spontaneous breathing trial performed before extubation may have influenced the results.<sup>27</sup> In addition, inclusion criteria identifying patients at high risk were different from previous studies.<sup>6,13,14</sup> However, international clinical practice guidelines specify that patients at high risk who may benefit from noninvasive ventilation are those older than 65 years or who have any underlying cardiac or respiratory disease.<sup>10</sup>

### Conclusions

In mechanically ventilated patients at high risk of extubation failure, the use of high-flow nasal oxygen with noninvasive ventilation immediately after extubation significantly decreased the risk of reintubation compared with high-flow nasal oxygen alone.

#### ARTICLE INFORMATION

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