

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients

## A Randomized Clinical Trial

Gonzalo Hernández, MD, PhD; Concepción Vaquero, MD; Paloma González, MD; Carles Subira, MD; Fernando Frutos-Vivar, MD; Gemma Rialp, MD; Cesar Laborda, MD; Laura Colinas, MD; Rafael Cuenca, MD; Rafael Fernández, MD, PhD

**IMPORTANCE** Studies of mechanically ventilated critically ill patients that combine populations that are at high and low risk for reintubation suggest that conditioned high-flow nasal cannula oxygen therapy after extubation improves oxygenation compared with conventional oxygen therapy. However, conclusive data about reintubation are lacking.

**OBJECTIVE** To determine whether high-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy for preventing reintubation in mechanically ventilated patients at low risk for reintubation.

**DESIGN, SETTING, AND PARTICIPANTS** Multicenter randomized clinical trial conducted between September 2012 and October 2014 in 7 intensive care units (ICUs) in Spain. Participants were 527 adult critical patients at low risk for reintubation who fulfilled criteria for planned extubation. Low risk for reintubation was defined as younger than 65 years; Acute Physiology and Chronic Health Evaluation II score less than 12 on day of extubation; body mass index less than 30; adequate secretions management; simple weaning; 0 or 1 comorbidity; and absence of heart failure, moderate-to-severe chronic obstructive pulmonary disease, airway patency problems, and prolonged mechanical ventilation.

**INTERVENTIONS** Patients were randomized to undergo either high-flow or conventional oxygen therapy for 24 hours after extubation.

**MAIN OUTCOMES AND MEASURES** The primary outcome was reintubation within 72 hours, compared with the Cochran-Mantel-Haenszel  $\chi^2$  test. Secondary outcomes included postextubation respiratory failure, respiratory infection, sepsis and multiorgan failure, ICU and hospital length of stay and mortality, adverse events, and time to reintubation.

**RESULTS** Of 527 patients (mean age, 51 years [range, 18-64]; 62% men), 264 received high-flow therapy and 263 conventional oxygen therapy. Reintubation within 72 hours was less common in the high-flow group (13 patients [4.9%] vs 32 [12.2%] in the conventional group; absolute difference, 7.2% [95% CI, 2.5% to 12.2%];  $P = .004$ ). Postextubation respiratory failure was less common in the high-flow group (22/264 patients [8.3%] vs 38/263 [14.4%] in the conventional group; absolute difference, 6.1% [95% CI, 0.7% to 11.6%];  $P = .03$ ). Time to reintubation was not significantly different between groups (19 hours [interquartile range, 12-28] in the high-flow group vs 15 hours [interquartile range, 9-31] in the conventional group; absolute difference, -4 [95% CI, -54 to 46];  $P = .66$ ). No adverse effects were reported.

**CONCLUSIONS AND RELEVANCE** Among extubated patients at low risk for reintubation, the use of high-flow nasal cannula oxygen compared with conventional oxygen therapy reduced the risk of reintubation within 72 hours.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT01191489

JAMA. doi:10.1001/jama.2016.2711  
Published online March 15, 2016.

← Editorial

← Related article

+ Supplemental content at  
jama.com

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Gonzalo Hernández, MD, PhD, Department of Critical Care Medicine, Hospital Virgen de la Salud, Mezquite nº12, 6ªA, 28045 Madrid, Spain (ghernandezm@telefonica.net).

**Section Editor:** Derek C. Angus, MD, MPH, Associate Editor, JAMA (angusdc@upmc.edu).

Oxygenation impairment after planned extubation is frequent and commonly corrected with conventional oxygen therapy delivered via either nasal prongs or Venturi masks, with fraction of inspired oxygen ( $F_{IO_2}$ ) and flow targeted to the degree of hypoxemia. Attempts to prevent postextubation respiratory failure have succeeded only for specific causes of reintubation (laryngeal edema<sup>1</sup> and hypercapnic respiratory failure in patients with chronic obstructive pulmonary disease<sup>2</sup>). Preventive noninvasive positive-pressure ventilation has failed to mitigate postextubation respiratory failure in the general population of critically ill patients,<sup>3</sup> although 2 randomized trials found evidence for its effectiveness in specific subgroups of patients with high-risk factors for reintubation.<sup>4,5</sup>

Technological improvements have enabled high-flow oxygen therapy to be delivered through nasal cannula. This mode now not only allows constant  $F_{IO_2}$  during peak inspiratory flow but also confers benefits such as a low level of continuous positive airway pressure<sup>6</sup> with increased end-expiratory lung volume<sup>7</sup> and reduced work of breathing, partly through intrinsic positive end-expiration pressure compensation and dead space washout.<sup>8</sup> The inspired gases are warmed and humidified, improving comfort and possibly reducing airway inflammation,<sup>9</sup> leading to improved drainage of respiratory secretions.<sup>10</sup>

Clinical studies in general populations of critically ill patients have found that high-flow therapy during the acute phase of respiratory failure improves oxygenation, survival,<sup>11</sup> tolerance and comfort,<sup>9,10</sup> and ease of respiratory secretions drainage.<sup>12</sup> High-flow therapy after extubation has demonstrated clinical benefits in specific populations such as preterm infants<sup>13</sup> and patients undergoing cardiac surgery.<sup>14</sup> Recently, Maggiore et al<sup>10</sup> suggested that high-flow therapy after planned extubation decreased the reintubation rate in a general population of critical patients, but the benefits observed in the general population might be mainly attributable to improvements in high-risk patients.

This study aimed to determine whether high-flow oxygen therapy immediately after planned extubation would reduce the need for reintubation compared with standard oxygen therapy in patients at low risk for reintubation.

## Methods

From September 2012 to October 2014, the randomized clinical trial was carried out in 7 intensive care units (ICUs) in Spain. The ethics committee at each hospital and the departments of health of the regional governments with which these hospitals are affiliated (Madrid, Castilla-la Mancha, Catalonia, and Balearic Islands) approved the study protocol (protocol available in Supplement 1). All patients or their relatives provided written informed consent, and none received a stipend.

### Patients

All adult patients receiving mechanical ventilation longer than 12 hours were eligible. Patients were recruited when ready for scheduled extubation after tolerating a spontaneous breath-

ing trial (eAppendix 1 in Supplement 2), provided they met the criteria for low risk of reintubation: younger than 65 years<sup>4,5</sup>; absence of heart failure as the primary indication for mechanical ventilation<sup>4,5</sup>; absence of moderate-to-severe chronic obstructive pulmonary disease<sup>15</sup>; Acute Physiology and Chronic Health Evaluation (APACHE) II score less than 12 points on day of extubation<sup>4,5</sup>; body mass index less than 30 (calculated as weight in kilograms divided by height in meters squared)<sup>2,16</sup>; absence of airway patency problems, including high risk of developing laryngeal edema (eAppendix 2 in Supplement 2)<sup>5</sup>; ability to manage respiratory secretions (adequate cough reflex or suctioning <2 times within 8 hours before extubation)<sup>5,17</sup>; simple weaning (eAppendix 3 in Supplement 2)<sup>5</sup>; fewer than 2 comorbidities (eAppendix 4 in Supplement 2)<sup>5</sup>; and no prolonged mechanical ventilation, defined as longer than 7 days.<sup>18</sup> Patients who had do-not-resuscitate orders, had tracheostomies, or were accidentally extubated or self-extubated were excluded. Patients who were hypercapnic during the spontaneous breathing trial were also excluded, because most physicians preferred to use preventive noninvasive ventilation instead of ordinary oxygen or high-flow therapy.<sup>2</sup>

At inclusion, demographic variables (age, sex, APACHE II score within first 24 hours after admission) and primary diagnosis were recorded. At extubation, the following variables were recorded: arterial blood gas levels, APACHE II score, and administration of steroids. In the 72 hours after extubation, the following variables were recorded: extubation-related complications, nasal septum and skin trauma as surrogates for adverse events, reasons for reintubation, and time to reintubation in hours. Patients were followed up until discharge from the hospital. Length of stay in the ICU and in the hospital and status at discharge from the hospital were recorded.

### Weaning Protocol

The clinical weaning protocol included daily screening for weaning readiness according to the following criteria<sup>19</sup>: recovery from the precipitating illness; respiratory criteria ( $P_{aO_2}$ : $F_{IO_2}$  ratio >150 mm Hg with  $F_{IO_2} \leq 0.4$ , positive end-expiratory pressure <8 cm H<sub>2</sub>O, and arterial pH >7.35); and clinical criteria (absence of electrocardiographic signs of myocardial ischemia, no vasoactive drugs or only low doses of dopamine [ $<5 \mu\text{g}/\text{kg}/\text{min}$ ], heart rate <140/min, hemoglobin >8 g/dL, temperature <38°C, no need for sedatives, presence of respiratory stimulus, and appropriate spontaneous cough). Patients fulfilling these criteria underwent a spontaneous breathing trial with either T-tube or 7 cm H<sub>2</sub>O of pressure support for 30 to 120 minutes. Standard criteria for failure of the spontaneous breathing trial were used (eAppendix 1 in Supplement 2). Patients who tolerated the spontaneous breathing trial were reconnected with the previous ventilator settings for rest and clinical evaluation of airway patency, respiratory secretions, and upper airway obstruction (eAppendix 2 in Supplement 2).

### Randomization

Before scheduled extubation, patients who passed the spontaneous breathing trial were randomized to receive conventional oxygen therapy or high-flow therapy by concealed allocation with a random-number generator (constant permuted

blocks of 10) through a telephone call center. Randomization was stratified by hospitals.

### Interventions

High-flow oxygen therapy (Optiflow; Fisher & Paykel Healthcare) was applied immediately after extubation through nasal cannula. Flow was initially set at 10 L/min and titrated upward in 5-L/min steps until patients experienced discomfort. Temperature was initially set to 37°C, unless reported too hot by patients, and  $\text{FIO}_2$  was regularly adjusted to target peripheral capillary oxygen saturation ( $\text{SpO}_2$ ) greater than 92%. After 24 hours, high-flow therapy was stopped and, if necessary, patients received conventional oxygen therapy.

Conventional oxygen therapy was applied continuously through nasal cannula or nonrebreather facemask, and oxygen flow was adjusted to maintain  $\text{SpO}_2$  greater than 92%.

Both groups were treated by the same medical, nursing, and respiratory therapy staff (excluding the investigators) and received similar medical management. Assisting physicians could not be blinded to the study group. To reduce this unavoidable bias, investigators did not participate in clinical decisions, and statistical analyses were performed in a blinded fashion.

### Outcomes

The primary outcome was reintubation within 72 hours after extubation. Predefined criteria for immediate respiratory-related reintubation included any of the following major clinical events: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, psychomotor agitation inadequately controlled by sedation, massive aspiration, persistent inability to remove respiratory secretions, heart rate less than 50/min with loss of alertness, or severe hemodynamic instability unresponsive to fluids and vasoactive drugs. Patients also were reintubated for persistent postextubation respiratory failure (defined in the next paragraph; see also eAppendix 5 in Supplement 2) or for nonrespiratory reasons (ie, without fulfilling postextubation respiratory failure criteria), such as urgent surgery or a low level of consciousness (decrease in Glasgow Coma Scale [GCS] score  $>2$  points or GCS score  $<9$  points) with  $\text{PaCO}_2$  less than 45 mm Hg.

Secondary outcomes were postextubation respiratory failure and respiratory infection (ventilator-associated pneumonia or ventilator-associated tracheobronchitis; see eAppendix 6 in Supplement 2). Postextubation respiratory failure was defined as the presence of any of the following criteria within 72 hours of extubation: respiratory acidosis ( $\text{pH} < 7.35$  with  $\text{PaCO}_2 > 45$  mm Hg),  $\text{SpO}_2$  less than 90% or  $\text{PaO}_2$  less than 60 mm Hg at  $\text{FIO}_2$  greater than 0.4, respiratory rate greater than 35/min, decreased level of consciousness (defined as a decrease in GCS score  $>1$  point), agitation, or clinical signs suggestive of respiratory muscle fatigue, increased work of breathing (eg, the use of respiratory accessory muscles, paradoxical abdominal motion, or retraction of the intercostal spaces), or both.<sup>20</sup> Delayed reintubation was considered the main safety concern, and time to reintubation was measured as a safety surrogate. Rescue therapy with noninvasive mechanical ventilation for postextubation respiratory failure was strongly discouraged.

Additional secondary outcomes included sepsis, multiorgan failure, ICU and hospital length of stay and mortality, time to reintubation, and adverse effects (study protocol, Supplement 1).

### Statistical Analysis

Based on a previous study, the absolute reduction in reintubation rate was estimated at 8%, from a basal rate of 13%.<sup>21</sup> In an effort to achieve 80% power to detect that difference, a sample size of 260 patients in each group of the study was considered adequate for a 2-sided test, an  $\alpha$  level of 5%, and a maximum tolerated patient loss rate of 15%. All analyses were performed on an intention-to-treat basis. Kaplan-Meier curves were plotted to assess the time from extubation to reintubation and compared by means of the log-rank test.

To assess the probability of reintubation, the Cochran-Mantel-Haenszel  $\chi^2$  test stratified according to recruiting hospital was used. To test whether the marginal odds ratio (OR) of high-flow therapy was similar to the OR conditioned to covariables, a multivariable logistic regression was used. The independent variables tested in the model were high-flow oxygen therapy, length of mechanical ventilation, hospital, and all the variables associated with reintubation that had  $P$  values less than .10 (eAppendix 7 in Supplement 2, bottom table). The analysis of the recruiting center effect included contingency tables according to center, analyzing the association between reintubation and center with the Cochran-Mantel-Haenszel test, and the OR homogeneity with the Breslow-Day test.

Analysis of secondary outcomes and post hoc analyses (eAppendix 8 in Supplement 2) used Fisher exact test,  $t$  test, Mann-Whitney  $U$  test, or Cochran-Mantel-Haenszel  $\chi^2$  tests (stratified for hospitals) as appropriate. The number needed to treat was calculated using the Newcombe-Wilson method. Confidence intervals for comparison of medians were calculated with the reference method.

The 2-sided level of significance was set at .05. The analysis included a simple sequentially multiple test to adjust for multiple comparisons for all secondary outcomes.<sup>22</sup> SPSS version 13.0 (SPSS Inc) was used for all statistical analyses.

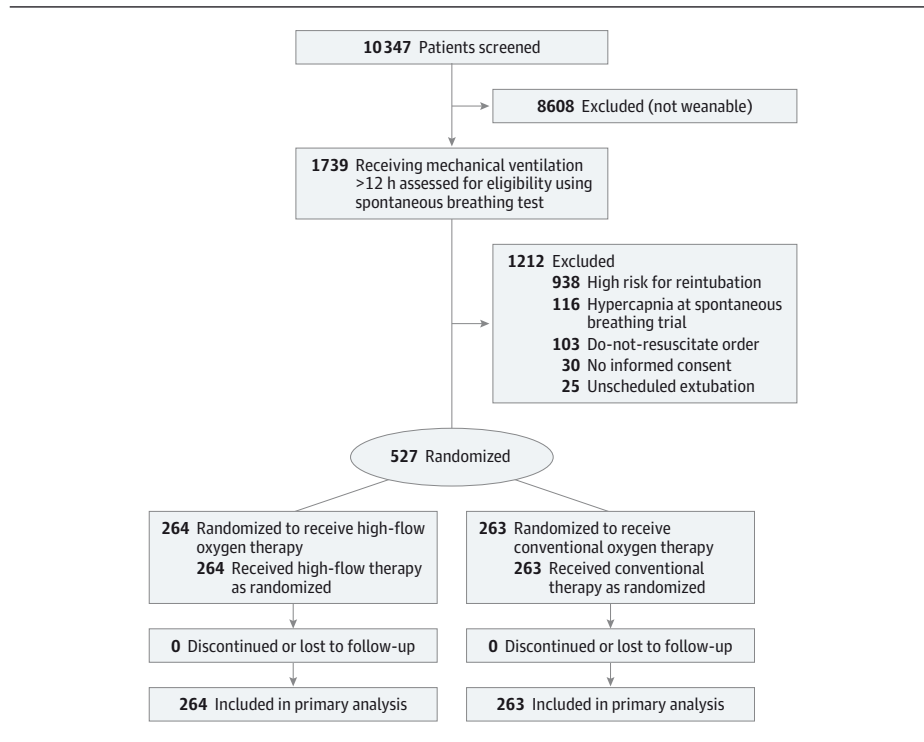
## Results

During the study period, 1739 weanable patients receiving mechanical ventilation for longer than 12 hours were identified; of these, 527 (30%) were randomized: 264 to the high-flow group and 263 to the conventional group (Figure 1). There were no dropouts from the study. Demographic and clinical characteristics of patients in the 2 groups were similar (Table 1), except for a lower incidence of neurologic comorbidity in the high-flow group (7.8% vs 12.9%), although mean GCS score at extubation was similar between groups (13 [SD, 1] vs 13 [SD, 1]).

### Primary Outcome

All patients were followed up for 72 hours, either in the ICU or on the ward. Reintubation within 72 hours was lower in the high-flow group: 13 patients (4.9%) vs 32 patients (12.2%) in the conventional group (absolute difference, 7.2% [95% CI,

Figure 1. Flow of Participants in a Study of Postextubation High-Flow Nasal Cannula Oxygen Therapy and Reintubation in Low-Risk Patients



2.5% to 12.2%];  $P = .004$ ). This difference was mainly attributable to a lower incidence of respiratory-related reintubation in the high-flow group: 1.5% vs 8.7% in the conventional group (absolute difference, 7.2% [95% CI, 3.6% to 11.4%];  $P = .001$ ) (Table 2 and Figure 2).

In the multivariable analysis, high-flow therapy was independently and inversely associated with all-cause reintubation (OR, 0.32 [95% CI, 0.16 to 0.66]) (eAppendix 7 in Supplement 2, top table) and respiratory-related reintubation (OR, 0.17 [95% CI, 0.06 to 0.51]). The number of patients needed to treat to prevent 1 reintubation with high-flow therapy was 14 (95% CI, 8 to 40). The statistical analysis was repeated after excluding the 7 reintubations secondary to laryngeal edema (4.9% vs 9.8%,  $P = .04$ ).

### Secondary Outcomes

Postextubation respiratory failure was less common in the high-flow group: 22 patients (8.3%) vs 38 patients (14.4%) in the conventional group (absolute difference, 6.1% [95% CI, 0.7% to 11.6%];  $P = .03$ ). Differences in other secondary outcomes were not statistically significant between the 2 groups (Table 2 and Table 3).

After adjusting all secondary outcomes for multiple comparisons, only  $\text{FIO}_2$  12 hours after extubation ( $P < .001$ ), laryngeal edema requiring reintubation ( $P = .02$ ), and respiratory-causes reintubation ( $P = .02$ ) remained statistically significant.

Differences in the median time to reintubation were not statistically significant between the 2 groups, for either all reintubations (19 hours [interquartile range {IQR}, 12-28] in the high-flow group vs 15 hours [IQR, 9-31] in the conventional

group; absolute difference,  $-4$  [95% CI,  $-54$  to  $46$ ];  $P = .66$ ) or for respiratory-related reintubations (18 hours in the high-flow group [IQR, 10-28] vs 17 hours [IQR, 9-30] in the conventional group; absolute difference, 7.2% [95% CI, 3.6% to 11.4%];  $P = .10$ ). Figure 2 shows the Kaplan-Meier curves for all-causes-related reintubations. After the 72-hour follow-up period, patients were reintubated only for surgical procedures; none of these patients had respiratory failure or extubation failure.

The difference in the median ICU length of stay was not statistically significant (6 days [IQR, 2-8] in the high-flow group vs 6 days [IQR, 2-9] in the conventional group; absolute difference, 0 [95% CI,  $-10$  to  $24$ ];  $P = .29$ ).

Compared with reintubated patients, successfully extubated patients had shorter duration of mechanical ventilation (1 [range, 1-2] vs 3 [range, 1-3] days; absolute difference, 2 [95% CI,  $-2$  to  $4$ ];  $P < .001$ ), shorter ICU stay (2 [range, 1-3] vs 11 [range, 3-15] days; absolute difference, 9 [95% CI,  $-28$  to  $10$ ];  $P < .001$ ), and shorter hospital stay (9 [range, 5-14] vs 13 [range, 8-21] days; absolute difference, 4 [95% CI,  $-31$  to  $23$ ];  $P = .005$ ). No adverse effects were detected: all patients tolerated the high-flow nasal cannulae, and no nasal mucosa or skin traumas were reported.

### Discussion

The main finding of this study was that high-flow oxygen significantly reduced the reintubation rate in critically ill patients at low risk for extubation failure. The reintubation rate in the control group receiving conventional oxygen therapy



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

Characteristic	Oxygen Therapy, No. (%)	
	High-Flow (n = 264)	Conventional (n = 263)
Age, mean (SD), y	51 (13.1)	51.8 (12.2)
Men	164 (62.1)	153 (58.2)
APACHE II at ICU admission, median (IQR) <sup>b</sup>	14 (9-16)	13 (9-17)
APACHE II at extubation, median (IQR) <sup>b</sup>	7 (6-9)	7 (5-9)
Length of mechanical ventilation before extubation, median (IQR), d	1 (1-3)	2 (1-4)
Corticosteroids >12 h before extubation	6 (2.7)	7 (3.2)
<b>Comorbidities<sup>c</sup></b>		
Arterial hypertension	43 (16.3)	37 (14.1)
Neurologic disease	20 (7.6)	34 (12.9)
Other respiratory disease	24 (9.1)	25 (9.5)
Heart disease	20 (7.6)	23 (8.7)
Cancer	23 (8.7)	18 (6.8)
Body mass index >25 <sup>d</sup>	21 (8)	14 (5.3)
Diabetes mellitus	16 (6.1)	14 (5.3)
Hepatic disease	11 (4.2)	9 (3.4)
Mild COPD	8 (3)	5 (1.9)
Renal failure	3 (1.1)	4 (1.5)
Other comorbid conditions	15 (5.7)	20 (7.6)
<b>Diagnosis at Admission<sup>e</sup></b>		
Medical	175 (66.3)	196 (74.5)
Respiratory primary failure	43 (16.3)	44 (16.7)
ARDS <sup>f</sup>	4 (1.5)	11 (4.2)
Respiratory tract infection	11 (4.2)	10 (3.8)
Exacerbated COPD	3 (1.1)	2 (.8)
Airway patency problem	10 (3.8)	6 (2.3)
Other	15 (5.7)	15 (5.7)
Nonrespiratory primary failure	132 (50)	152 (57.8)
Cardiologic	21 (8)	21 (8)
Neurologic	69 (26.1)	86 (32.7)
Other	42 (15.9)	45 (17.1)
Trauma	44 (16.7)	39 (14.8)
Traumatic brain injury	31 (11.7)	17 (6.5)
Surgical	131 (49.6)	120 (45.6)
Scheduled surgery	45 (17)	35 (13.3)
Urgent surgery	86 (32.6)	85 (32.3)
<b>Physiologic Variables From Spontaneous Breathing Trial Prior to Extubation, Mean (SD)</b>		
Pao <sub>2</sub> :Fio <sub>2</sub> , mm Hg	227 (25)	237 (34)
Paco <sub>2</sub> , mm Hg	39 (2.4)	38 (2.9)
Arterial pH	7.4 (.3)	7.4 (.2)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; Fio<sub>2</sub>, fraction of inspired oxygen; IQR, interquartile range.

<sup>a</sup> See also eAppendix 9 in Supplement 2.

<sup>b</sup> APACHE II score was calculated from 17 variables. Scores range from 0 to 71 points, with higher scores indicating more severe disease.

<sup>c</sup> Comorbidities were categorized based on the Charlson Comorbidity Index (see eAppendix 4 in Supplement 2).

<sup>d</sup> Calculated as weight in kilograms divided by height in meters squared.

<sup>e</sup> Patients can have more than 1 diagnosis.

<sup>f</sup> Defined according to the American European Consensus Definition. These patients are included under current mild ARDS diagnosis.

(12.2%) was similar to rates from previous reports in general critically ill populations.<sup>23</sup> However, few data are available about reintubation rates in selected populations without high-risk factors for extubation failure; reported reintubation rates in low-risk groups range from 5%<sup>15</sup> to 13%,<sup>24,25</sup> mainly depending on the criteria selected to represent high risk for reintubation. By contrast, the reintubation rate for patients receiving conventional oxygen therapy in clinical trials in populations selected to include only patients at high risk for reintubation (22%-24%)<sup>4,5</sup> are higher.

The proportion of patients reintubated for nonrespiratory-related causes depends mainly on the case mix, which varies widely among ICUs, and has not usually been reported in clinical studies. In the present study, up to 30% of reintubations were related to nonrespiratory causes, because the case mix included high proportions of postsurgical and neurocritical patients. After excluding these causes, the reintubation rate in the present study was low enough to be comparable to what is expected in a low-risk population (1.5% vs 8.7%).

Delaying intubation or reintubation can be deleterious. In 2004, Esteban et al<sup>26</sup> reported higher mortality in patients randomized to receive noninvasive mechanical ventilation, mostly attributable to delayed reintubation, raising concerns that noninvasive mechanical ventilation might increase the risk of postextubation respiratory failure. More recently, Kang et al<sup>27</sup> found worse outcomes in patients in whom high-flow therapy delayed intubation more than 48 hours. However, in the present study, preventive high-flow therapy did not delay reintubation (time to reintubation, 19 [IQR, 12-28] hours in the high-flow group vs 15 [IQR, 9-31] hours in the conventional group). This lack of delay is probably attributable to the low-risk population and the protocol, which limited high-flow therapy to 24 hours after extubation. High-flow therapy increases comfort and oxygenation<sup>10</sup> and may disguise respiratory distress for an extended period, so the 24-hour limit probably helped physicians appreciate undertreated respiratory distress at an early stage. The downside of the 24-hour time limit is that improvements in secretions management favored by gas conditioning in high-flow therapy may be time-dependent<sup>10</sup> (the longer the time under high flow, the greater the expected improvement). However, the results confirmed that 24-hour high-flow therapy was enough to reduce the rate of reintubation for the inability to clear secretions in low-risk patients.

The use of high-flow therapy was restricted to 24 hours after extubation because 24 hours is the standard monitoring time before ICU discharge in the study environment, and at the time patients were recruited, there were no devices able to apply high-flow therapy without a source of medical air, which is not always available in the ward. However, the optimal length of high-flow therapy is unknown. Maggiore et al<sup>10</sup> randomized a general population of critically ill patients to receive either high-flow therapy or conventional therapy for 48 hours. They found better oxygenation in the high-flow group starting from 24 hours after initiating treatment and achieved a low reintubation rate (3.8%) in the high-flow group. On the other hand, as suggested by Kang et al,<sup>27</sup> applying high-flow therapy up to 7 days according to clinical response could lead to delayed intubation associated with worse outcome. Until addi-

Table 2. Primary and Secondary Outcomes

Variable	Oxygen Therapy		Difference Between Groups (95% CI)	P Value
	High-Flow (n = 264)	Conventional (n = 263)		
<b>Primary Outcome</b>				
All-cause reintubation, No. (%)	13 (4.9)	32 (12.2)	7.2 (2.5 to 12.2)	.004 <sup>a</sup>
<b>Secondary Outcomes</b>				
Postextubation respiratory failure, No. (%)	22 (8.3)	38 (14.4)	6.1 (0.7 to 11.6)	.03 <sup>a</sup>
Respiratory infection, No. (%)	6 (2.3)	13 (4.9)	2.7 (-0.6 to 6.2)	.07 <sup>a</sup>
Ventilator-associated tracheobronchitis	3 (1.1)	7 (2.6)	1.5 (-1.0 to 4.4)	.22 <sup>a</sup>
Ventilator-associated pneumonia	3 (1.1)	6 (2.3)	1.2 (-1.3 to 3.9)	.31 <sup>a</sup>
<b>Causes of postextubation respiratory failure, No. (%)</b>				
Respiratory acidosis <sup>c</sup>	1 (4.5)	4 (10.5)		
Hypoxia <sup>c</sup>	7 (31.8)	6 (15.8)		
Unbearable dyspnea	9 (40.9)	14 (28.9)		.10 <sup>b</sup>
Decreased level of consciousness	2 (9)	0		
Inability to clear secretions	3 (13.6)	14 (36.8)		
<b>Reasons for reintubation, No. (%)</b>				
<b>Respiratory causes for reintubation</b>				
Cardiorespiratory arrest	0	1 (0.4)		
Agitation	1 (0.4)	0		
Inability to clear secretions	0	5 (1.9)		
Hemodynamic impairment <sup>d</sup>	1 (0.4)	1 (0.4)		
Persistent postextubation respiratory failure	2 (0.8)	16 (6)		.02 <sup>b</sup>
<b>Nonrespiratory causes for reintubation</b>				
Surgery	4 (1.5)	6 (2.3)		
Low level of consciousness <sup>e</sup>	5 (1.9)	3 (1.1)		
Sepsis, No. (%)	2 (0.7)	1 (0.4)	-0.4 (-2.4 to 1.5)	.99 <sup>b</sup>
Multiorgan failure, No. (%)	1 (0.4)	0	-0.4 (-2.1 to 1.1)	.99 <sup>b</sup>
Time to reintubation, median (IQR), h	19 (12 to 28)	15 (9 to 31)	-4 (-54 to 46)	.66 <sup>f</sup>
ICU length of stay, median (IQR), d	6 (2 to 8)	6 (2 to 9)	0 (-10 to 24)	.29 <sup>f</sup>
Hospital length of stay, median (IQR), d	11 (6 to 15)	12 (6 to 16)	4 (-28 to 32)	.76 <sup>f</sup>
ICU mortality	3 (1.1)	3 (1.1)	0 (-2.3 to 2.3)	.99 <sup>a</sup>
Hospital mortality	10 (3.8)	13 (5)	1.2 (-2.5 to 4.9)	.94 <sup>a</sup>
Adverse events, nasal mucosa and skin trauma	0	NA	NA	NA

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NA, not applicable.

<sup>a</sup> Cochran-Mantel-Haenszel  $\chi^2$  test stratified according to recruiting hospital.

<sup>b</sup> Fisher exact test or  $\chi^2$ .

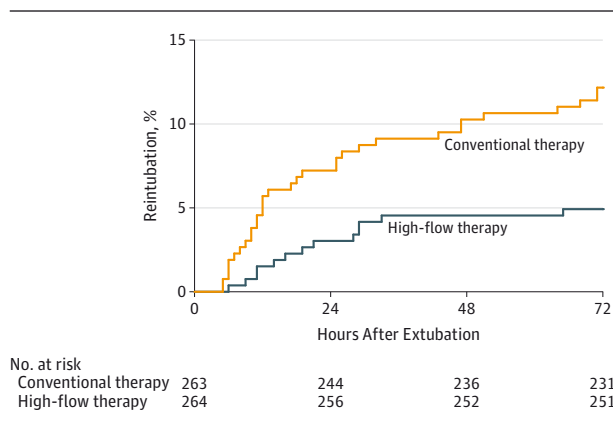
<sup>c</sup> Respiratory acidosis: pH less than 7.35 with PaCO<sub>2</sub> greater than 45 mm Hg; hypoxia: SpO<sub>2</sub> less than 90% or PaO<sub>2</sub> less than 60 mm Hg at Fio<sub>2</sub> greater than 0.4.

<sup>d</sup> Heart rate less than 50/min with loss of alertness, or severe hemodynamic instability (systolic blood pressure <90 mm Hg for >30 min) unresponsive to fluids and vasoactive drugs.

<sup>e</sup> Criteria for reintubation secondary to low level of consciousness: decrease in Glasgow Coma Scale score more than 2 points or score less than 9 points with PaCO<sub>2</sub> less than 45 mm Hg.

<sup>f</sup> Mann-Whitney U.

Figure 2. Kaplan-Meier Analysis of Time From Extubation to Reintubation



tional studies using high-flow therapy after extubation become available, the length of high-flow therapy should be targeted by predefined reintubation criteria, but the efficacy probably could be increased with longer use of high-flow therapy after extubation.

High-flow therapy favors successful extubation in different ways. High-flow therapy improves oxygenation,<sup>10</sup> and the lower rate of reintubation secondary to hypoxia in the high-flow group corroborates this finding. High-flow oxygen also seems to reduce other causes of respiratory failure such as increased work of breathing and respiratory muscle fatigue,<sup>6-8</sup> which are frequently associated with reintubation secondary to hypoxia. Another way in which high-flow therapy improves extubation outcome is by conditioning the inspired gas.<sup>9</sup> Maggiore et al<sup>10</sup> demonstrated that high-flow oxygen improves the management of respiratory secretions, and the lower rate of reintubations secondary to up-

Table 3. Exploratory Outcomes and Between-Group Differences in Physiologic Variables

	Oxygen Therapy		Difference Between Groups (95% CI)	P Value
	High-Flow (n = 264)	Conventional (n = 263)		
<b>Exploratory Outcomes, No. (%)</b>				
Respiratory-causes reintubation <sup>a</sup>	4 (1.5)	23 (8.7)	7.2 (3.6 to 11.4)	.001 <sup>b</sup>
Immediate postextubation stridor	2 (0.9)	9 (4.1)	2.7 (0.1 to 5.7)	.04 <sup>c</sup>
Laryngeal edema requiring reintubation <sup>a</sup>	0	7 (3.1)	2.7 (0.7 to 5.4)	.001 <sup>c</sup>
<b>Physiologic Variables, Mean (SD)</b>				
FiO <sub>2</sub> 12 h after extubation	0.32 (0.08)	0.4 (0.09)	-0.08 (-0.09 to -0.07)	<.001 <sup>d</sup>
High-flow oxygen therapy 12 h after extubation, L/min	30.9 (7.6)	NA	NA	NA
Pao <sub>2</sub> :Fio <sub>2</sub> , mm Hg <sup>e</sup>	105 (32)	108 (34)	-3 (-9 to 3)	.57
Paco <sub>2</sub> , mm Hg <sup>e</sup>	37 (8)	36 (6)	1 (-0.2 to 2.2)	.84
Arterial pH <sup>e</sup>	7.37 (0.3)	7.4 (0.4)	-0.3 (-0.09 to 0.03)	.49

Abbreviations: FIO<sub>2</sub>, fraction of inspired oxygen; NA, not applicable.

<sup>a</sup> Secondary outcomes with statistically significant differences after adjusting by multiple statistical tests of hypotheses related to secondary outcomes.<sup>22</sup>

<sup>b</sup> Cochran-Mantel-Haenszel  $\chi^2$  test stratified according to recruiting hospital.

<sup>c</sup> Fisher exact test or  $\chi^2$ .

<sup>d</sup> t test.

<sup>e</sup> Analysis including postextubation respiratory failure and reintubated patients only.

per airway obstruction in the high-flow group in the present study reinforces that result. Maggiore et al's<sup>10</sup> findings support the idea that gas conditioning probably alleviates inflammation of the tracheal mucosa after transglottic intubation; in the present study, the application of totally conditioned high-flow oxygen through a nasal cannula at extubation (aimed to block the entrance of dry and cold air in the patients' native airway), and the lower rate of upper airway obstruction, suggests this strategy was effective, lending weight to this idea. However, given the short use of high-flow oxygen after extubation in this study, other possible mechanisms that are not time dependent cannot be ruled out. To exclude a bias in these results secondary to a difference in the number of patients with stridor, the statistical analysis was repeated after excluding these patients, confirming that there is no heterogeneity in the odds ratio.

Although lower reintubation rates would be expected to shorten ICU and hospital stays,<sup>4,19</sup> no differences in these secondary outcomes were found, probably because the percentage of reintubated patients was too low to affect outcome variables in the entire group. The high rate of non-respiratory-related reintubation and the high proportion of neurocritical patients also might account for this lack of difference in these outcomes. Differences in mortality were not expected, owing to the low mortality rate in this low-risk population. However, the wide confidence intervals observed in the analysis of secondary and exploratory outcomes—probably related to an inadequate sample size, not calculated for these outcomes—limits definite conclusions about these results.

### Study Limitations

To select patients at low risk for reintubation, high-risk factors were selected mainly based on those reported in studies by Nava et al<sup>5</sup> and Ferrer et al<sup>4</sup> using noninvasive mechanical ventilation to prevent postextubation respiratory failure as well as those identified in other studies.<sup>3,14-17,28-30</sup> Although a model to accurately predict extubation failure has not been prospectively validated, mainly because various factors can simultaneously influence the outcome of extubation, many risk factors (eg, abundant secretions, weak cough, low level of consciousness at the time of extubation, advanced age, underlying chronic cardiac or respiratory disease, and length of mechanical ventilation)<sup>17,28,29</sup> have been confirmed in several

studies, including randomized trials.<sup>4,5</sup> The protocol excluding patients who fulfilled any of the 10 criteria for high risk for reintubation can reasonably be expected to select patients at low risk for reintubation. The only variables not included in the definition of high risk were physiologic variables at extubation, and Thille et al<sup>31</sup> recently demonstrated again that physiologic variables at extubation are not associated with the risk of extubation failure.

The greater proportion of patients with medical diagnoses at admission in the control group could have some effect on the results; however, a sensitivity analysis showed no difference (eAppendix 8 in Supplement 2). The case mix in the present study included a high percentage of surgical and neurocritical patients, and this could account for the high proportion of non-respiratory-related reintubations and the great improvement in reintubation secondary to inability to clear respiratory secretions. However, another sensitivity analysis rejected any significant impact of neurologic diseases in the results (see eAppendix 8 in Supplement 2). In addition, these post hoc analyses suggest that the benefit could vary with the patient's diagnosis at admission.

The final decision to reintubate was determined by clinical criteria, and the single most relevant reason for reintubation was recorded. However, reintubation can sometimes be attributed to simultaneous causes, making it difficult to interpret these results.

Attending physicians could not be blinded to the study group. To reduce this unavoidable bias, investigators were excluded from clinical decisions. Another limitation is that FIO<sub>2</sub> was not truly reliable in the control group. Most patients were receiving oxygen via face mask immediately after extubation, and many of them were switched to nasal cannula in the 24 hours after extubation; however, the type of oxygen delivery device was not recorded after 24 hours.

### Conclusions

Among extubated patients at low risk for reintubation, the use of high-flow nasal cannula oxygen compared with conventional oxygen therapy reduced the risk of reintubation within 72 hours.

## ARTICLE INFORMATION

**Published Online:** March 15, 2016.  
doi:10.1001/jama.2016.2711.

**Author Affiliations:** Hospital Virgen de la Salud, Toledo, Spain (Hernández, Colinas); Hospital Universitario Ramón y Cajal, Madrid, Spain (Vaquero); Hospital Universitario Infanta Sofía, Madrid, Spain (González); Hospital Sant Joan de Deu-Fundació Althaia, Manresa, Spain (Subira, Fernández); Hospital Universitario de Getafe, Madrid, Spain (Frutos-Vivar); CIBER Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain (Frutos-Vivar, Fernández); Hospital Son Llatzer, Palma de Mallorca, Spain (Rialp); Hospital Universitario Vall d'Hebron, Barcelona, Spain (Laborda); Research Unit, Medical Council, Toledo, Spain (Cuenca); Universitat Internacional de Catalunya, Spain (Fernández).

**Author Contributions:** Dr Hernández had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Hernández, Fernández.  
**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Hernández, Laborda, Colinas, Cuenca.

**Critical revision of the manuscript for important intellectual content:** Hernández, Vaquero, Gonzalez, Subira, Frutos-Vivar, Rialp, Colinas, Cuenca, Fernández.

**Statistical analysis:** Hernández, Cuenca, Fernández.  
**Obtained funding:** Laborda.

**Administrative, technical, or material support:** Hernández, Vaquero, Subira.

**Study supervision:** Hernández, Gonzalez, Fernández.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

**Funding/Support:** Fisher & Paykel Healthcare Ltd provided air-oxygen blenders to 2 of the study intensive care units.

**Role of the Funder/Sponsor:** The study received no external funding, and Fisher & Paykel had no other involvement in the study, including design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

**Additional Contributions:** We thank all of the patients and medical and nursing staff for their cooperation. John Giba, BSc, received financial compensation for editing the English in the manuscript.

## REFERENCES

- Jaber S, Jung B, Chanques G, Bonnet F, Marret E. Effects of steroids on reintubation and post-extubation stridor in adults: meta-analysis of randomised controlled trials. *Crit Care*. 2009;13(2):R49.
- Ferrer M, Sellarés J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet*. 2009;374(9695):1082-1088.
- Glossop AJ, Shephard N, Bryden DC, Mills GH. Non-invasive ventilation for weaning, avoiding reintubation after extubation and in the postoperative period: a meta-analysis [published correction appears in *Br J Anaesth*. 2013;110(1):164]. *Br J Anaesth*. 2012;109(3):305-314.
- Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med*. 2006;173(2):164-170.
- Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Crit Care Med*. 2005;33(11):2465-2470.
- Parke RL, McGuinness SP. Pressures delivered by nasal high flow oxygen during all phases of the respiratory cycle. *Respir Care*. 2013;58(10):1621-1624.
- Riera J, Pérez P, Cortés J, Roca O, Masclans JR, Rello J. Effect of high-flow nasal cannula and body position on end-expiratory lung volume: a cohort study using electrical impedance tomography. *Respir Care*. 2013;58(4):589-596.
- Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. *Intensive Care Med*. 2013;39(2):247-257.
- Roca O, Riera J, Torres F, Masclans JR. High-flow oxygen therapy in acute respiratory failure. *Respir Care*. 2010;55(4):408-413.
- 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(3):282-288.
- Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23):2185-2196.
- Kilgour E, Rankin N, Ryan S, Pack R. Mucociliary function deteriorates in the clinical range of inspired air temperature and humidity. *Intensive Care Med*. 2004;30(7):1491-1494.
- Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med*. 2013;369(15):1425-1433.
- Stéphan F, Barrucand B, Petit P, et al; BiPOP Study Group. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA*. 2015;313(23):2331-2339.
- Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med*. 2011;39(12):2612-2618.
- El-Solh AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. *Eur Respir J*. 2006;28(3):588-595.
- Salam A, Tilluckdharry L, Amoateng-Adjepong Y, Manthous CA. Neurologic status, cough, secretions and extubation outcomes. *Intensive Care Med*. 2004;30(7):1334-1339.
- Vallverdú I, Calaf N, Subirana M, Net A, Benito S, Mancebo J. Clinical characteristics, respiratory functional parameters, and outcome of a two-hour T-piece trial in patients weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1998;158(6):1855-1862.
- Boles JM, Bion J, Connors A, et al. Weaning from mechanical ventilation. *Eur Respir J*. 2007;29(5):1033-1056.
- Doorduyn J, van Hees HWH, van der Hoeven JG, Heunks LMA. Monitoring of the respiratory muscles in the critically ill. *Am J Respir Crit Care Med*. 2013;187(1):20-27.
- Hernandez G, Vaquero C, Garcia S, et al. High-flow conditioned oxygen therapy for prevention of reintubation in critically-ill patients: a preliminary cohort study. Abstract presented at: European Society of Intensive Care Medicine 25th Annual Congress; October 13-17, 2012; Lisbon, Portugal. Abstract A-254.
- Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6:65-70.
- 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(2):220-230.
- Funk GC, Anders S, Breyer MK, et al. Incidence and outcome of weaning from mechanical ventilation according to new categories. *Eur Respir J*. 2010;35(1):88-94.
- Peñuelas O, Frutos-Vivar F, Fernández C, et al; Ventila Group. Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. *Am J Respir Crit Care Med*. 2011;184(4):430-437.
- Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350(24):2452-2460.
- Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med*. 2015;41(4):623-632.
- Saugel B, Rakette P, Hapfelmeier A, et al. Prediction of extubation failure in medical intensive care unit patients. *J Crit Care*. 2012;27(6):571-577.
- Brown CV, Daigle JB, Foulkrod KH, et al. Risk factors associated with early reintubation in trauma patients: a prospective observational study. *J Trauma*. 2011;71(1):37-41.
- Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. *Am J Respir Crit Care Med*. 2000;161(5):1530-1536.
- Thille AW, Boissier F, Ben Ghezala H, Razazi K, Mekontso-Dessap A, Brun-Buisson C. Risk factors for and prediction by caregivers of extubation failure in ICU patients: a prospective study. *Crit Care Med*. 2015;43(3):613-620.