ORIGINAL ARTICLE

High-Flow Versus VenturiMask Oxygen Therapy to Prevent Reintubation in Hypoxemic Patients after Extubation

A Multicenter Randomized Clinical Trial

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Abstract

Rationale: When compared with VenturiMask after extubation, high-flow nasal oxygen provides physiological advantages.

Objectives: To establish whether high-flow oxygen prevents endotracheal reintubation in hypoxemic patients after extubation, compared with VenturiMask.

Methods: In this multicenter randomized trial, 494 patients exhibiting Pa_{O_2}:FI_{O_2} ratio ⩽ 300 mm Hg after extubation were randomly assigned to receive high-flow or VenturiMask oxygen, with the possibility to apply rescue noninvasive ventilation before reintubation. High-flow use in the VenturiMask group was not permitted.

Measurements and Main Results: The primary outcome was the rate of reintubation within 72 hours according to predefined criteria, which were validated *a posteriori* by an independent adjudication committee. Main secondary outcomes included reintubation rate at 28 days and the need for rescue noninvasive ventilation according to predefined criteria. After intubation criteria validation ($n = 492$ patients), 32 patients (13%) in the high-flow group and 27 patients (11%) in the VenturiMask group required reintubation at 72 hours (unadjusted odds ratio, 1.26 [95% confidence interval (CI), 0.70–2.26]; $P = 0.49$). At 28 days, the rate of reintubation was 21% in the high-flow group and 23% in the VenturiMask group (adjusted hazard ratio, 0.89 [95% CI, 0.60–1.31]; $P = 0.55$). The need for rescue noninvasive ventilation was significantly lower in the high-flow group than in the VenturiMask group: at 72 hours, 8% versus 17% (adjusted hazard ratio, 0.39 [95% CI, 0.22–0.71]; $P = 0.002$) and at 28 days, 12% versus 21% (adjusted hazard ratio, 0.52 [95% CI, 0.32–0.83]; $P = 0.007$).

Conclusions: Reintubation rate did not significantly differ between patients treated with VenturiMask or high-flow oxygen after extubation. High-flow oxygen yielded less frequent use of rescue noninvasive ventilation.

Clinical trial registered with www.clinicaltrials.gov (NCT02107183).

Keywords: weaning; oxygen therapy; nasal high-flow oxygen; acute respiratory failure; noninvasive ventilation

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A complete list of RINO Trial Study Group members may be found in the online supplement.

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Data sharing: Data can be made available by the corresponding author (S.M.M.) upon a reasonable request. The study protocol and the statistical analysis plan are available as supplementary material to this article.

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In mechanically ventilated patients recovering from respiratory failure, extubation is performed when the acute phase of the disease has resolved and predetermined criteria are met, but it is not always successful (1, 2). Reintubation is needed in around 15% of cases and is associated with increased risk of complications and worse mortality (3–5). Treatment of postextubation hypoxemia is essential in such a context, with oxygen therapy commonly administered to improve oxygen delivery (6, 7).

In the ICU, high-flow nasal oxygen has been tested as first-line treatment in patients experiencing acute hypoxemic respiratory failure, for preoxygenation during endotracheal intubation, and to facilitate weaning from mechanical ventilation, with promising results (8–14).

High-flow nasal oxygen appears as effective as noninvasive ventilation in patients experiencing or at high risk of respiratory failure after extubation (15, 16) and preemptive nasal high-flow oxygen, compared with low-flow oxygen, has been shown to prevent reintubation among critically ill patients at low risk of reintubation (17, 18).

VenturiMasks provide gas mixture at higher flows than the low-flow devices used for oxygen therapy as control treatments in previous randomized studies. We previously demonstrated that, compared with VenturiMask after extubation in hypoxemic patients recovering from respiratory failure, high-flow nasal oxygen improves oxygenation and reduces Pa_{CO_2}, respiratory rate, and discomfort (19). Whether these physiological benefits translate into improved extubation weaning outcome remains to be established.

We conducted a multicenter, randomized trial to determine whether high-flow nasal oxygen may reduce the reintubation rate of critically ill patients experiencing hypoxemia after extubation, compared with VenturiMask oxygen therapy.

Methods

Study Design

The RINO (Reintubation Rate after Oxygen Therapy: Impact of Nasal High-Flow versus VenturiMask Oxygen Therapy on Weaning Outcome) trial is an investigator-initiated, multicenter, randomized, two-arm, open-label study conducted between June 2014 and October 2016 in 13 ICUs in Italy (4), France (7), Spain (1), and Greece (1). The study was sponsored by Fisher and Paykel Healthcare (New Zealand). The investigators and the sponsor had access to patients' data. Statistical analysis was conducted independently of the sponsor (*see* Statistical Analysis section). All sites had experience with the use of both VenturiMasks and high-flow nasal oxygen. The institutional review board of the coordinator center (Catholic University of The Sacred Heart, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy) reviewed and approved the study protocol before trial initiation (no. 12634/13 on December 5, 2013). By in-site beginning of enrollment, each local ethics committee reviewed and approved the study protocol. Each enrolled patient or next of kin provided written informed consent to participate in the trial. The study was conducted in accordance with the declaration of Helsinki and was registered on April 8, 2014 on www.clinicaltrials.gov (NCT02107183).

Participants

All adult intubated patients mechanically ventilated for at least 48 hours in the ICU and eligible for undergoing a spontaneous breathing trial were eligible for enrollment.

To avoid delays in the administration of study treatments, written informed consent to study participation was preferentially obtained before spontaneous breathing trial or immediately after extubation.

Readiness to undergo a spontaneous breathing trial was defined by the presence of the following criteria (1, 20):

- improvement or resolution of the underlying cause of acute respiratory failure;
- normal sensorium (alertness and ability to communicate);
- correction of arterial hypoxemia ($Pa_{O_2} \geq 60$ mm Hg at a $FI_{O_2} \leq 40\%$ with positive end-expiratory pressure ≤ 5 cm H_2O);
- absence of fever ($\geq 38^{\circ}C$) or sepsis;
- blood hemoglobin concentration ≥ 7 g/dl;
- hemodynamic stability without cardiac ischemia or arrhythmias.

At a Glance Commentary

Scientific Knowledge on the Subject: Weaning from mechanical ventilation and extubation are critical procedures in mechanically ventilated patients, as weaning failure and reintubation occur in up to 10–30% of cases and are associated with increased mortality. In one randomized trial, preemptive high-flow nasal oxygen, as compared to low-flow oxygen, has been shown to prevent reintubation among critically ill patients at low risk of weaning failure. The use of noninvasive ventilation was rigorously discouraged in both groups, despite some evidence indicating that its use among selected patients may prevent reintubation when oxygen therapy fails. VenturiMasks provide gas mixture at higher flows than the low-flow devices used for oxygen therapy as control treatment in that study. Compared to VenturiMask after extubation in hypoxemic patients, high-flow nasal oxygen provides physiological advantages. Whether these physiological benefits translate into improved weaning outcome remains to be established.

What This Study Adds to the Field: In this open-label randomized trial, 494 patients with hypoxemia after extubation were randomly assigned to receive high-flow nasal or VenturiMask oxygen, with the possibility to apply rescue noninvasive ventilation before reintubation. We found that re-intubation rate at 72 hours and 28 days did not significantly differ between groups. Use of high-flow nasal oxygen yielded to less frequent use of rescue noninvasive ventilation.

The spontaneous breathing trial was conducted in both groups according to clinical practice at each center. Failure or success was defined according to predetermined criteria (*see* online supplement E1) (1). In failing patients, mechanical ventilation was resumed with settings provided by the attending physician, and new spontaneous breathing trials were performed on a daily basis whether the predefined criteria were met. Succeeding patients were extubated and received oxygen therapy via VenturiMask (OS/60K, FIAB), with $F_{I_{O_2}}$ = 31% and oxygen flow set according to manufacturer's recommendation (8 L/min).

Patients were considered eligible for inclusion in the study if they showed hypoxemia within 120 minutes after extubation. Hypoxemia was assessed during oxygen therapy via VenturiMask 31% and was defined by Pa_{O_2}:$F_{I_{O_2}}$ < 300 mm Hg or by a peripheral oxygen saturation (Sp_{O_2}) to nominal $F_{I_{O_2}}$ ratio < 300% (with Sp_{O_2} < 98%) (21).

The exclusion criteria were the presence of a tracheostomy, pregnancy, and the need for prophylactic noninvasive ventilation immediately after extubation, according to the following predetermined criteria (20, 22, 23): *1*) more than three consecutive failures of a spontaneous breathing trial; *2*) Pa_{CO_2} > 45 mm Hg with respiratory rate > 25 breaths/min before the spontaneous breathing trial.

Inclusion of patients with compensated hypercapnia (i.e., Pa_{CO_2} > 45 mm Hg with pH ⩾ 7.35) without objective signs of respiratory distress during the spontaneous breathing trial (no use of accessory muscles and respiratory rate < 25 breaths/min) was permitted.

Procedures

Enrolled patients were randomized in a 1:1 ratio to receive VenturiMask or high-flow nasal oxygen.

Randomization was performed within 120 minutes after extubation, immediately after the oxygenation criterion validation. A computer-generated randomization scheme managed by a centralized web-based system allocated patients to each group. Randomization was stratified according to the cause of ICU admission (medical vs. surgical or trauma), age (⩽65 vs. >65 yr), and the presence of hypercapnia at inclusion (Pa_{CO_2} ⩽ 45 mm Hg vs. >45 mm Hg). Patients had to undergo the allocated treatment within 120 minutes from the time of extubation.

Patients received oxygen through VenturiMask (OS/60K, FIAB) or high-flow nasal oxygen with the Optiflow system (Fisher and Paykel). In both groups, set $F_{I_{O_2}}$ was titrated to maintain a Sp_{O_2} between 92% and 98%, or between 88% and 95% in hypercapnic patients, for the entire study period.

In patients receiving high-flow nasal oxygen, gas flow rate was initially set at the highest value (50–60 L/min) and eventually diminished in case of intolerance; the temperature of the heated humidifier (Fisher and Paykel Healthcare) was set at 37°C (absolute humidity delivered 44 mg H_2O/L) and then eventually reduced to enhance patient comfort (24).

Among patients receiving VenturiMask, oxygen was passively humidified and pure oxygen flow was set depending on the nominal $F_{I_{O_2}}$, as stated by manufacturer's recommendation. $F_{I_{O_2}}$ was continuously titrated to obtain the Sp_{O_2} target. No crossover to high-flow nasal oxygen was allowed in the VenturiMask group.

In the high-flow group, weaning from the device could be attempted after 12 hours, if set $F_{I_{O_2}}$ was <40% and patient's respiratory rate was <25 breaths/min. Readiness to tolerate high-flow nasal oxygen discontinuation was established by progressively (steps of 10 L/min) lowering gas flow to 10 L/min, while keeping $F_{I_{O_2}}$ unchanged. Intolerance to flow decrease was defined as persistent (>5 min) drop in the Sp_{O_2} >3% or <92% (88% in hypercapnic patients), and/or an increase in respiratory rate >20% or >25 breaths/min at any time during this procedure. Conversely, weaning was considered successful if Sp_{O_2} remained >92% (or 88% in hypercapnic patients) and the respiratory rate <25 breaths/min while the patient was receiving nasal flow of 10 L/min for 30 minutes. In this latter case, high-flow nasal oxygen could be replaced by the VenturiMask; otherwise, the treatment was continued. In patients who were successfully weaned from high-flow nasal oxygen, the treatment could be resumed at any time in case of Sp_{O_2} < 92%, respiratory rate > 25 breaths/min, presence of respiratory distress, and/or according to the prescription of the attending physician. At ICU discharge, all enrolled patients still requiring oxygen administration received oxygen therapy with VenturiMask.

In both arms, standard care, which included respiratory physiotherapy, was delivered according to the clinical practice of each institution.

Treatment Failure

Extubation failure was defined as the need for endotracheal reintubation within 72 hours after extubation and before discharge from the ICU. To avoid any delay in reintubation and to standardize treatments

in both groups, the decision to intubate was based on predefined criteria, that included the presence of unbearable dyspnea and at least one of the following (8, 25–27):

- hypercapnia with respiratory acidosis (arterial pH $\leq$ 7.25 with Pa_{CO_2} > 45 mm Hg);
- changes in mental status, making nursing care impossible and requiring sedation;
- Sp_{O_2} < 85% or Pa_{O_2} < 45 mm Hg despite oxygen therapy with FI_{O_2} > 50%;
- hypotension, with a systolic blood pressure < 70 mm Hg for >30 minutes despite fluid resuscitation and/or use of vasopressors;
- copious secretions that were not adequately cleared or that were associated with acidosis, hypoxemia, or changes in mental status;
- intolerance to rescue noninvasive ventilation.

All the reasons for reintubation were recorded.

Among patients experiencing respiratory failure during the assigned treatment, a trial of rescue noninvasive ventilation before reintubation was allowed in both arms, if predetermined criteria were met (supplement E2). Noninvasive ventilation settings and interfaces were chosen by the attending physician.

Given that the final decision to reintubate was made by the attending physician who could not be blinded to study treatments, an adjudication committee reviewed *a posteriori* (blindly to assigned treatments) the records of all intubated patients to ascertain that the decision to intubate was unbiased and in accordance with the criteria of the protocol. The adjudication committee consisted of three clinicians with expertise in the field (F. Roche Campo, J.-C. M. Richard, and A. Mercat), who were not involved in the study.

Measurements

All data were recorded on the electronic case report form and managed by a centralized web system (data manager: FerrarioDati). Patient demographics were collected at study entry, together with the Simplified Acute Physiologic Score II (SAPSII), the main comorbidities, the cause and length of ICU stay, the reason and duration of invasive mechanical ventilation, the Sequential Organ Failure Assessment (SOFA) score on the day of enrollment, and the physiological parameters certifying the successful spontaneous breathing trial and the oxygenation criterion needed for inclusion in the study.

Daily arterial blood gases and the episodes of oxygen desaturation (defined as Sp_{O_2} < 92%) were collected; arterial blood gas analysis was performed before noninvasive ventilation initiation or reintubation in all failing patients to certify the fulfillment of the required criteria.

Outcomes

The primary outcome was the rate of endotracheal reintubation within 72 hours from randomization and before ICU discharge in the modified intention-to-treat population, which included all intubated patients but those for whom the reasons of reintubation were not deemed adherent to the predefined criteria by the adjudication committee. Secondary endpoints included: the rate of endotracheal reintubation within 72 hours in the intention-to-treat population, need for endotracheal intubation up to 28 days from randomization, need for noninvasive ventilation within 72 hours and up to 28 days from enrollment, length of ICU and hospital length of stay, the need for ICU readmission, and ICU and in-hospital mortality. Safety endpoints included the time from randomization to endotracheal reintubation, the incidence of the prespecified events leading to reintubation, and rescue noninvasive ventilation use. Exploratory outcomes included ventilator-free days on a 28-day basis, the number of episodes of hypoxemia per patient (Sp_{O_2} < 90%) during the assigned treatments, and 90-day mortality. Moreover, to handle the effect of the competing risk of death on the endotracheal reintubation rate, we report a *post hoc* exploratory composite outcome including in-hospital reintubation or death without reintubation.

All endpoints except for the primary outcome measure were analyzed on an intention-to-treat basis.

Statistical Analysis

Previous data indicate that the reintubation rate in hypoxemic patients receiving VenturiMask after extubation is 18% (19). We calculated that the enrollment of 225 patients per group (total: 450 patients) would provide an 80% power to detect a 9% absolute reduction in the rate of the primary outcome in high-flow nasal oxygen group, with an α of 0.05. Enrollment of 500 patients was foreseen to take into account a 10% attrition rate due to protocol violations, absence of objective criteria to define the primary endpoint, crossover, and drop-outs.

All data are displayed as frequencies, means (SD), or medians (interquartile range [IQR]), as appropriate, and tabulated descriptively by study group. Analysis on the primary endpoint and on categorical secondary endpoints was performed using a Fisher exact test. Kaplan-Meier survival analyses regarding the time to reintubation and time to the need for rescue noninvasive ventilation in the two groups were performed: the graphical representation shows no evidence against the assumption of proportionality. Ordinal qualitative variables or nonnormal quantitative variables were compared with the Wilcoxon sum of ranks (Mann-Whitney *U*) test, and results are displayed as medians (IQR). Quantitative normal variables were compared with the Student's *t* test, and results are displayed as means $\pm$ SD.

Multivariate analyses were conducted on all prespecified secondary endpoints, which included time-to-event data: backward elimination procedure on the Cox proportional hazards regression model was applied considering the assigned treatment as fixed (nonoptional) term and all other possible predictors (supplement E3) as optional terms. All other possible predictors were prespecified. The Cox model was iteratively fitted, and the optional predictor with the highest *P* value was eliminated at each step, until all remaining (if any) optional predictors were simultaneously significant at $P \leq 0.05$. *Post hoc* exploratory analyses on the rate of endotracheal reintubation were conducted in the following subgroups: patients having received mechanical ventilation because of acute respiratory failure; patients with age $\geq$ 65 years; patients with mechanical ventilation duration $\geq$ 7 days; patients with SAPSII $\geq$ 40 at ICU admission; patients with SOFA score $\geq$ 4 at enrollment; patients with compensated hypercapnia (Pa_{CO_2} > 45 mm Hg with pH $\geq$ 7.35 at study inclusion).

All analyses other than the one on the primary outcome should be considered exploratory and intended as hypothesis generating. Two-sided *P* value $\leq$ 0.05 was

considered statistically significant. There were no missing data for the primary, secondary, and safety endpoints. All statistical analyses were conducted in the R statistical computing environment (R Foundation for Statistical Computing).

Results

Between June 1, 2014 and October 31, 2016, 1,385 patients were screened for undergoing weaning from mechanical ventilation; among 557 patients eligible for inclusion in the study, 517 underwent randomization (Figure 1). After secondary exclusion by the independent data manager of 2 patients who withdrew consent, 4 who did not receive assigned treatments within 2 hours after extubation, 15 who had significant inconsistencies in the recorded data, and 2 who had been erroneously deemed eligible despite Pa_{O_2}:FI_{O_2} ratio > 300 mm Hg, 494 patients completed the trial and were included in the intention-to-treat analysis: 243 patients were assigned to the high-flow group and 251 patients to the VenturiMask group.

Characteristics at Inclusion

The characteristics of the patients at enrollment are displayed in Table 1. Patients had been mechanically ventilated mainly because of acute respiratory failure (220 patients, 45%), for a median time of 5 days (IQR, 3–8 d). While on VenturiMask with a nominal FI_{O_2} of 31% after extubation, their mean (±SD) Pa_{O_2}:FI_{O_2} ratio was 228 ± 46 mm Hg.

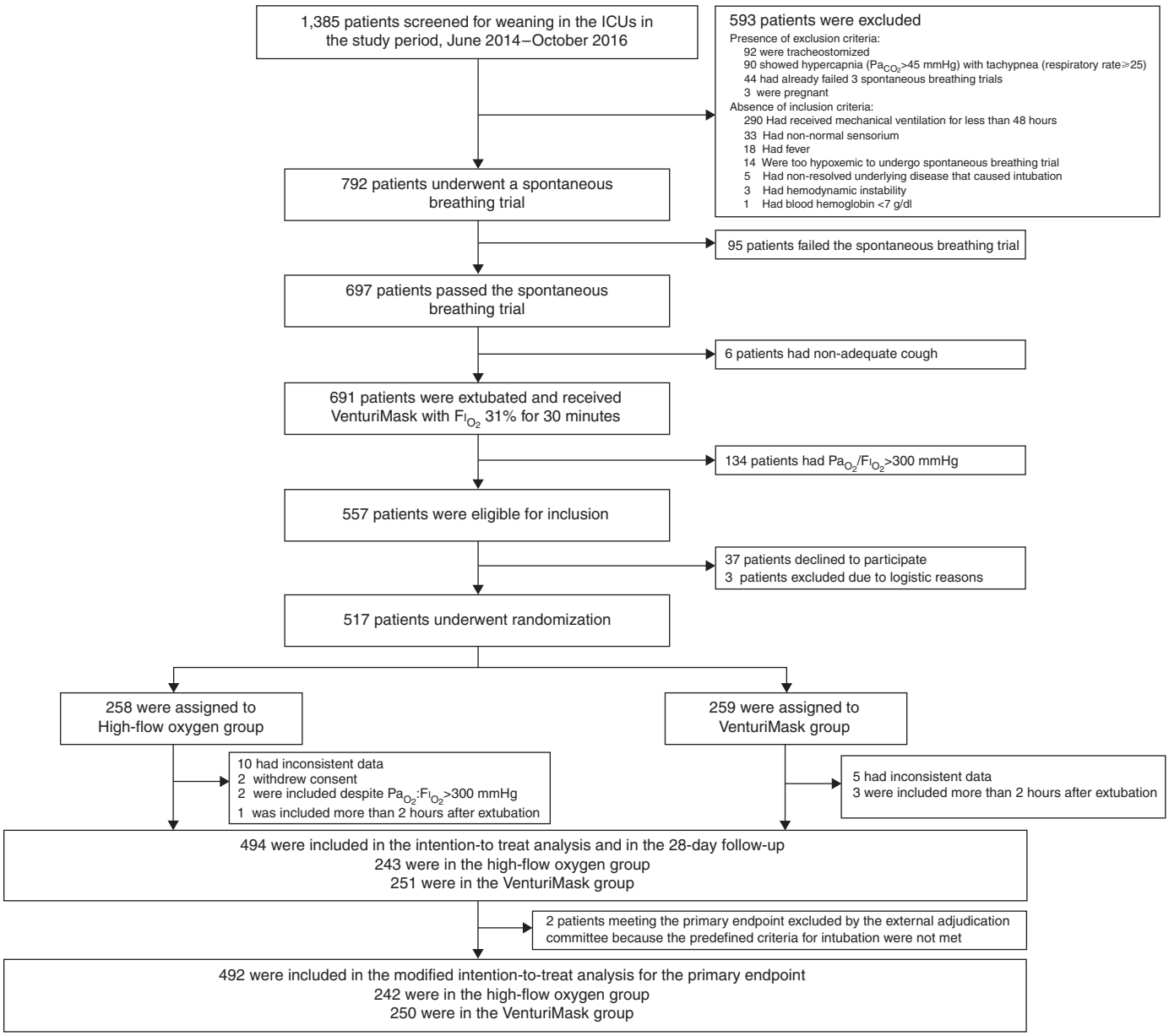

Figure 1. Consort diagram of the RINO (Reintubation Rate after Oxygen Therapy: Impact of Nasal High-Flow versus VenturiMask Oxygen Therapy on Weaning Outcome) trial.

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

Characteristic	VenturiMask ($n = 251$)	High-Flow Nasal Oxygen ($n = 243$)
Age, yr	63 ± 14	62 ± 15
Male sex	166 (66)	171 (70)
Body mass index*	27 ± 6	27 ± 5
SAPSII†	42 ± 18	40 ± 16
Type of admission in the ICU		
Medical	172 (69)	165 (68)
Surgical or trauma	79 (31)	78 (32)
Current smoking	49 (20)	48 (20)
Comorbidities		
Cardiac failure	34 (14)	29 (12)
Myocardial infarction	14 (6)	15 (6)
Renal failure	40 (16)	30 (12)
Chronic respiratory failure	30 (12)	29 (12)
Liver cirrhosis	23 (9)	20 (8)
HIV	7 (3)	3 (1)
Multiple transfusions	7 (3)	9 (4)
Use of corticosteroids	27 (11)	26 (11)
Chemotherapy	15 (6)	9 (4)
Reason for mechanical ventilation		
Acute respiratory failure	102 (41)	118 (49)
Brain injury or altered consciousness	50 (20)	48 (20)
Surgery	45 (18)	29 (12)
Circulatory failure	32 (13)	22 (9)
Trauma	10 (4)	17 (7)
Duration of ICU stay before enrollment, d	6 (3–9)	6 (3–9)
Duration of mechanical ventilation before enrollment, d	6 (3–9)	5 (3–8)
SOFA at enrollment	4 (3–7)	4 (3–6)
Heart rate at enrollment, beats/min	87 ± 19	85 ± 21
Arterial pressure at enrollment, mm Hg		
Systolic	133 ± 20	134 ± 21
Mean	89 ± 13	90 ± 14
Arterial blood gases at enrollment		
pH	7.46 ± 0.06	7.45 ± 0.05
Pa_{O_2}:F_{IO_2}, mm Hg‡	232 ± 49	225 ± 42
Pa_{CO_2}, mm Hg	38 ± 8	38 ± 7
Sp_{O_2}:F_{IO_2}§	306 ± 23	304 ± 22
VenturiMask F_{IO_2} at enrollment, %	31 ± 3	31 ± 3
Respiratory rate, breaths/min	21 (17–25)	20 (18–24)

Definition of abbreviations: SAPSII = Simplified Acute Physiology Score II; Sp_{O_2} = peripheral oxygen saturation.
Data are presented as mean ± SD, *n* (%), or median (interquartile range).
*The body mass index is the weight in kilograms divided by the square of the height in meters.
†The SAPSII 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.
‡Pa_{O_2}:F_{IO_2} was available for 476 patients: 245 in the VenturiMask group and 231 in the high-flow nasal oxygen group.
§Sp_{O_2}:F_{IO_2} was available for 417 patients: 211 in the VenturiMask group and 206 in the high-flow nasal oxygen group.

Treatments

The initial settings were as follows: in the VenturiMask group, nominal F_{IO_2} was 36 ± 12%; in the high-flow group, F_{IO_2} was 50 ± 23% with a gas flow rate of 45 ± 12 L/min. In the high-flow group, treatment was delivered before successful weaning for a median time of 28 hours (IQR, 23–58 h). No patient in the VenturiMask group received high-flow nasal oxygen.

Primary Endpoint

Primary and secondary outcomes are displayed in Table 2. Sixty-one patients (12%) were reintubated within 72 hours and before discharge from the ICU. Two patients (one in each group) were excluded from the modified intention-to-treat analysis on the primary endpoint, as the adjudication committee deemed that reintubation had not been performed because of the prespecified criteria of the protocol. In this cohort (492 patients), reintubation at 72 hours within the ICU stay was needed in 32 of 242 patients (13%) in the high-flow group and in 27 of 250 (11%) patients in the VenturiMask group, with an unadjusted odds ratio for the high-flow group of 1.26 (95% confidence interval [CI], 0.70–2.26) ($P = 0.49$) (Figure 2).

No significant intergroup differences in the rate of endotracheal intubation at 72 hours and 28 days were found in any of the analyzed subgroup of patients (*see* Table in supplement E4).

Secondary Endpoints

In the intention-to-treat population (494 patients), endotracheal reintubation within 72 hours and before ICU discharge was needed in 33 patients (14%) in the high-flow group and in 28 patients (11%) in the VenturiMask group, with an unadjusted odds ratio for the high-flow group of 1.25 (95% CI, 0.71–2.23) ($P = 0.49$). This

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

Outcome	High-Flow Nasal Oxygen ($n = 243$)	VenturiMask ($n = 251$)	Odds Ratio or Mean Difference (95% CI)	*P* Value
Primary outcome				
Reintubation within 72 h. Modified intention-to-treat population (after the presence of intubation criteria were adjudicated by the external committee; $n = 492$ patients)	32 (13)	27 (11)	1.26 (0.70 to 2.26)	0.49
Secondary outcomes				
Reintubation within 72 h. Intention-to-treat population	33 (14)	28 (11)	1.25 (0.71 to 2.23)	0.49
Reintubation within 28 d	51 (21)	57 (23)	0.90 (0.58 to 1.42)	0.66
Need for rescue noninvasive ventilation within 72 h	20 (8)	42 (17)	0.45 (0.24 to 0.81)	0.004
Need for rescue noninvasive ventilation within 28 d	30 (12)	53 (21)	0.53 (0.31 to 0.88)	0.011
Duration of stay in the ICU, d	11 (7 to 21)	11 (7 to 20)	1 (−2 to 3)	0.56
Duration of stay in the hospital, d	32 (17 to 64)	33 (20 to 65)	1 (−4 to 6)	0.51
Need for ICU readmission	23 (9)	19 (8)	1.28 (0.64 to 2.55)	0.52
In-ICU mortality	12 (5)	16 (6)	0.76 (0.42 to 0.76)	0.56
In-hospital mortality	32 (13)	40 (16)	0.80 (0.47 to 1.37)	0.44
Safety endpoints				
Hours to reintubation	50 (16 to 91)	72 (21 to 165)	−31 (−78 to 16)	0.11
Incidence of prespecified events requiring reintubation within 72 h from extubation*				
Hypoxemia	16 (7)	16 (6)	1.04 (0.51 to 2.12)	>0.999
Hypercapnia	2 (1)	7 (3)	0.29 (0.06 to 1.41)	0.18
Inability to clear secretions	19 (8)	15 (6)	1.33 (0.66 to 2.69)	0.48
Intolerance to rescue treatment with noninvasive ventilation	2 (1)	5 (2)	0.41 (0.08 to 2.12)	0.45
Altered mental status	11 (5)	5 (2)	2.33 (0.80 to 6.82)	0.13
Incidence of prespecified events requiring rescue noninvasive ventilation use*				
Hypoxemia	24 (10)	32 (13)	0.75 (0.41 to 1.36)	0.32
Hypercapnia	9 (4)	8 (3)	1.17 (0.39 to 2.54)	0.81
Tachypnea	13 (5)	38 (15)	0.32 (0.16 to 0.64)	<0.001
Respiratory fatigue or distress	27 (11)	48 (19)	0.53 (0.31 to 0.90)	0.017
Exploratory outcomes				
Episodes of hypoxemia per patient ($Sp_{O_2} < 90\%$) during the stay in ICU	0 (0 to 0)	0 (0 to 0)	−0.1 (−0.2 to 0.1)	0.49
Ventilator-free days at 28 d	28 (25 to 28)	28 (23 to 28)	0 (−2 to 1)	0.34
90-d mortality	29 (12)	39 (16)	0.74 (0.42 to 1.27)	0.30
Reintubation or death without reintubation during the hospital stay	67 (28)	77 (31)	0.86 (0.58 to 1.27)	0.49

Definition of abbreviation: Sp_{O_2} = peripheral oxygen saturation.
Values are displayed as median (interquartile range) or *n* (%). There were no missing data among the two groups. All the calculations were unadjusted. Adjusted results are reported in the Results section of the manuscript. For nonnormal quantitative variables, comparison between groups was performed with the Mann-Whitney test. Comparisons between groups for qualitative variables were performed with the chi-square test or the Fisher exact test, as appropriate in agreement with tests assumptions.
*Each patient could develop one or more indications to endotracheal reintubation and rescue noninvasive ventilation. For all other endpoints, what is reported is the number of patients with the event rather than number of events.

difference remained not significant after adjustment for covariates (presence of kidney failure at inclusion), with an adjusted hazard ratio for the high-flow group of 1.19 (95% CI, 0.72–1.96) ($P = 0.51$).

At 28 days, endotracheal reintubation was needed in 51 patients (21%) in the high-flow group and in 57 patients (23%) in the VenturiMask group, with an unadjusted odds ratio for the high-flow group of 0.90 (95% CI, 0.71–2.23) ($P = 0.66$). This difference remained not significant after adjustment for covariates (Pa_{O_2}:FI_{O_2} at study inclusion and the duration of ICU stay before enrollment), with an adjusted hazard ratio for the high-flow group of 0.89 (95% CI, 0.60–1.31) ($P = 0.55$) (Figure 3).

The proportion of patients requiring rescue noninvasive ventilation within 72 hours and 28 days from enrollment was significantly lower in the high-flow group than in the VenturiMask group: at 72 hours, 20 patients (8%) versus 42 patients (17%), with an unadjusted odds ratio for the high-flow group of 0.45 (95% CI, 0.24–0.81) ($P = 0.004$); at 28 days, 30 patients (12%) versus 53 patients (21%), with an unadjusted odds ratio for the high-flow group of 0.45 (95% CI, 0.24–0.81) ($P = 0.011$). The need for rescue noninvasive ventilation remained significantly lower in the high-flow group after adjustment for covariates (72 h: Pa_{O_2}:FI_{O_2} at study inclusion and presence of HIV; 28 days: Pa_{O_2}:FI_{O_2} at study inclusion and SOFA score at enrollment), with an adjusted hazard ratio for the high-flow group of 0.39 (95% CI, 0.22–0.71) ($P = 0.002$) at 72 hours and 0.52 (95% CI, 0.32–0.83) ($P = 0.007$) at 28 days (Figures 2 and 3).

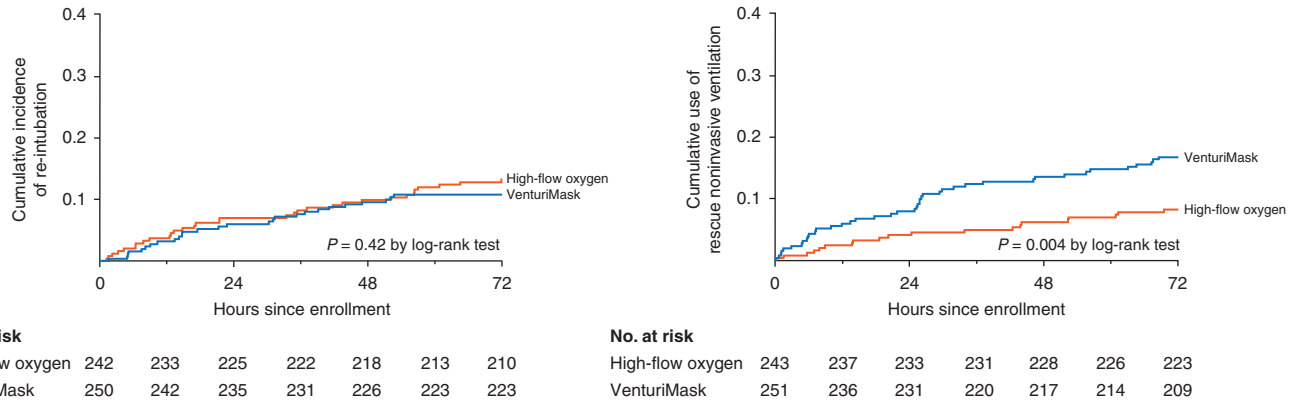

Figure 2. Left: Kaplan-Meier plots of the cumulative incidence of reintubation within 72 hours from enrollment and before ICU discharge in the modified intention-to-treat population (after intubation criteria were adjudicated by the external committee; $n = 492$ patients). Right: Kaplan-Meier plots of the cumulative use of rescue noninvasive ventilation within 72 hours from enrollment in the intention-to-treat population ($n = 494$ patients).

Among patients who received rescue noninvasive ventilation within 28 days from enrollment, the rate of subsequent endotracheal reintubation was 55% (29 of 53 treated patients) in the VenturiMask group and 53% (16 of 30 treated patients) in the high-flow group ($P > 0.99$).

The rate of in-hospital mortality was 13% in the high-flow group and 16% in the VenturiMask group, a difference that was statistically significant neither in the univariate analysis (unadjusted odds ratio for the high-flow group of 0.80 [95% CI, 0.47–1.37]; $P = 0.44$) nor after adjustment for covariates (age, SAPSII at ICU admission and Pa_{O_2}:FI_{O_2} at study inclusion), with an adjusted hazard ratio for the high-flow group of 0.84 (95% CI, 0.51–1.40).

Safety Endpoints

For reintubated patients, the median time from randomization to endotracheal reintubation was 50 hours (IQR, 16 to 91) in the high-flow group and 72 hours (IQR, 21 to 165) in the VenturiMask group, a difference that was not statistically significant (mean difference, −31 h [95% CI, −78 to 16 h]; $P = 0.11$).

Patients in the high-flow group required noninvasive ventilation less frequently than those receiving VenturiMask because of a statistically significantly lower incidence of tachypnea (5% vs. 15%; unadjusted odds ratio for the high-flow group of 0.32 [95% CI, 0.16–0.64]; $P < 0.001$) and fatigue or respiratory distress (11% vs. 19%, unadjusted odds ratio for the high-flow group of 0.53 [95% CI, 0.31–0.90]; $P = 0.017$) during the allocated treatment.

There were no statistically significant differences in any of other analyzed outcomes (Table 2).

Discussion

In this open-label, multicenter randomized trial involving patients who experienced hypoxemia after scheduled extubation in the ICU, the use of high-flow nasal oxygen did not result in a lower rate of extubation failure in comparison to VenturiMask oxygen therapy. Consistently, no effect was found on the length of intensive care and hospital stay or on all-cause mortality. Patients in the VenturiMask group, however, more often required rescue noninvasive ventilation.

The use of high-flow nasal oxygen, which delivers up to 60 L/min of an air/oxygen mixture actively conditioned by a heated humidifier through specifically designed nasal cannula, is becoming widespread (28, 29). The system, by matching patients' peak inspiratory flow, ensures accurate delivery of the set FI_{O_2} (30, 31), generates a flow-dependent upper airways

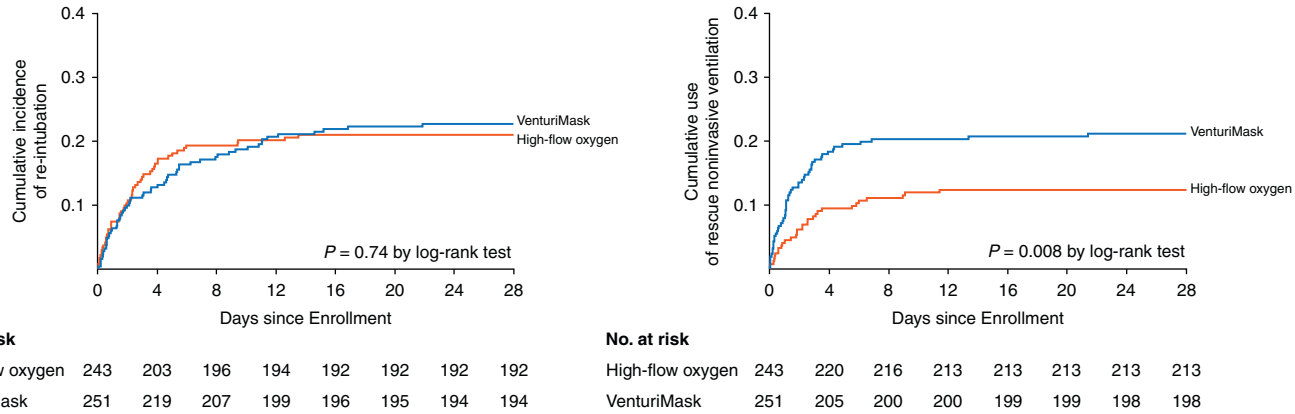

Figure 3. Left: Kaplan-Meier plots of the cumulative incidence of reintubation within 28 days from enrollment in the intention-to-treat population ($n = 494$ patients). Right: Kaplan-Meier plots of the cumulative use of rescue noninvasive ventilation within 28 days in the intention-to-treat population ($n = 494$ patients).

washout effect enhancing CO_2 clearance in the anatomical dead space (32), and optimizes tolerance through full gas conditioning and the comfortable interface (33–35). In addition, an air entrainment effect produced by a patient's expiration against the continuous gas flow generates a nasopharyngeal flow-dependent positive pressure, with values up to 5–6 cm H_2O reached at the end of expiration and when the mouth is closed (36–39). Compared with low-flow oxygen, high-flow nasal oxygen increases end-expiratory lung volume and Pa_{O_2}:$F_{I_{O_2}}$ ratio, reduces work of breathing, enhances CO_2 clearance, and optimizes compliance of the respiratory system, with the most benefit documented when the highest flows are used (36, 40–43).

Hernández and colleagues reported that, among critically ill patients at low risk of weaning failure, preemptive high-flow nasal oxygen after extubation prevents reintubation in comparison to low-flow oxygen (17). In that study, however, the use of noninvasive ventilation was rigorously discouraged in both groups; in our trial, extubation outcome might have been affected by the possibility of applying a rescue noninvasive ventilation trial in patients experiencing respiratory distress. Preemptive noninvasive ventilation in unselected patients after extubation can delay reintubation, with a detrimental effect on clinical outcome (44, 45), and is hence discouraged. However, its use among selected cohorts of patients from experienced teams may be of benefit (46), facilitating the weaning process in patients at high risk of reintubation while recovering from acute respiratory failure (47–52). Recent large studies support its use for treating hypoxemic patients after surgery and critically ill patients at high risk of reintubation in the ICU (47, 50, 51, 53). In our study, the use of high-flow nasal oxygen was associated with a less frequent need for a rescue treatment with noninvasive ventilation. Importantly, this intervention was applied based on prespecified criteria. The less-frequent use of rescue noninvasive ventilation in the high-flow group was due to lower incidence of tachypnea and respiratory fatigue during the treatment: respiratory muscle unloading and dyspnea relief are well-described effects of high-flow nasal oxygen. These mostly depend on the CO_2 washout from upper airways produced by the device, which reduces ventilation dead space (29, 54). Our findings are consistent with the results of the recent PROPER (Protocolized Post-Extubation Respiratory Support) trial, which showed that preemptive high-flow nasal oxygen in all patients does not reduce the rate of reintubation if escalation of noninvasive respiratory support (high-flow oxygen or noninvasive ventilation) is permitted in the control group (5).

High-flow nasal oxygen provides clinical benefits in the postextubation phase. Avoiding rescue noninvasive ventilation may improve patients' comfort, reduce personnel workload, and help save ventilator equipment.

All large randomized trials conducted to assess difference in efficacy between devices for oxygen therapy in the postextubation phase compared high-flow nasal with low-flow oxygen (12, 17, 55). VenturiMasks, thanks to the air entrainment effects, provide significantly higher outflows at predetermined $F_{I_{O_2}}$ than low-flow oxygen, especially when low $F_{I_{O_2}}$ is used (56). In our study, mean VenturiMask $F_{I_{O_2}}$ at treatment initiation was 36 $\pm$ 12%, and this should correspond to a total nominal gas outflow exceeding 30 L/min, according to manufacturer's specifications. Delivery of higher flows during VenturiMask oxygen therapy, compared with conventional low-flow devices, may have contributed to increase the rate of extubation success in the control group.

Our trial has several strengths that suggest that the results may be generalized to patients who are weaned after at least 48 hours of mechanical ventilation and exhibit hypoxemia after extubation in other ICUs. These include the multicenter design, the sealed randomization to the assigned strategy, a well-defined study population, the use of prespecified standardized criteria for both reintubation and the need for rescue noninvasive ventilation, and complete follow-up at 90 days.

Our study has limitations. The rate of endotracheal reintubation in the VenturiMask group was lower than that hypothesized in the sample size calculation, possibly making the study underpowered to detect smaller differences between groups. Also, submission of the manuscript for publication was delayed because of the shift of the sponsor's personnel in charge to follow the trial and by the surge of the coronavirus disease (COVID-19) pandemic.

In conclusion, compared with VenturiMask oxygen therapy in critically ill patients exhibiting hypoxemia after scheduled extubation, high-flow nasal oxygen does not reduce the rate of endotracheal reintubation. Use of high-flow nasal oxygen is associated with less-frequent need for rescue noninvasive ventilation. ■

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