ORIGINAL ARTICLE

Noninvasive Ventilation for Preoxygenation during Emergency Intubation

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ABSTRACT

BACKGROUND

Among critically ill adults undergoing tracheal intubation, hypoxemia increases the risk of cardiac arrest and death. The effect of preoxygenation with noninvasive ventilation, as compared with preoxygenation with an oxygen mask, on the incidence of hypoxemia during tracheal intubation is uncertain.

METHODS

In a multicenter, randomized trial conducted at 24 emergency departments and intensive care units in the United States, we randomly assigned critically ill adults (age, ≥18 years) undergoing tracheal intubation to receive preoxygenation with either noninvasive ventilation or an oxygen mask. The primary outcome was hypoxemia during intubation, defined by an oxygen saturation of less than 85% during the interval between induction of anesthesia and 2 minutes after tracheal intubation.

RESULTS

Among the 1301 patients enrolled, hypoxemia occurred in 57 of 624 patients (9.1%) in the noninvasive-ventilation group and in 118 of 637 patients (18.5%) in the oxygen-mask group (difference, −9.4 percentage points; 95% confidence interval [CI], −13.2 to −5.6; P<0.001). Cardiac arrest occurred in 1 patient (0.2%) in the noninvasive-ventilation group and in 7 patients (1.1%) in the oxygen-mask group (difference, −0.9 percentage points; 95% CI, −1.8 to −0.1). Aspiration occurred in 6 patients (0.9%) in the noninvasive-ventilation group and in 9 patients (1.4%) in the oxygen-mask group (difference, −0.4 percentage points; 95% CI, −1.6 to 0.7).

CONCLUSIONS

Among critically ill adults undergoing tracheal intubation, preoxygenation with noninvasive ventilation resulted in a lower incidence of hypoxemia during intubation than preoxygenation with an oxygen mask. (Funded by the U.S. Department of Defense; PREOXI ClinicalTrials.gov number, NCT05267652.)

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The PREOXI Investigators and members of the Pragmatic Critical Care Research Group are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Gibbs, Semler, Ginde, and Casey contributed equally to this article.

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More than 1.5 million critically ill adults undergo tracheal intubation each year in the United States.[1,2] Hypoxemia occurs during 10 to 20% of tracheal intubations in the emergency department or intensive care unit (ICU) and is associated with cardiac arrest and death.[3-7]

Preoxygenation, the administration of supplemental oxygen before induction of anesthesia, increases the content of oxygen in the lung at induction and decreases the risk of hypoxemia during the tracheal intubation procedure.[8,9] In current clinical care, most critically ill adults receive preoxygenation by means of an oxygen mask.[3,4,7] Oxygen masks are simple to set up and can deliver a fraction of inspired oxygen (FIO_2) as high as 100% under ideal conditions. However, oxygen masks do not provide positive pressure or ventilatory support, and the actual FIO_2 received may be as low as 50% when ambient air is entrained around a loose-fitting mask.[10] Noninvasive ventilation, also referred to as bilevel positive airway pressure, is an alternative to an oxygen mask for preoxygenation in critically ill adults. Noninvasive ventilation, which involves the use of a tight-fitting mask and a high gas flow, can deliver an FIO_2 of 100%, provide positive pressure, and support ventilation. However, noninvasive ventilation requires more time to set up and could potentially increase the risk of aspiration of gastric contents during intubation.[11,12]

Two small, randomized trials have compared noninvasive ventilation with oxygen masks for preoxygenation in critically ill adults. One trial suggested that the risk of hypoxemia was lower with noninvasive ventilation than with an oxygen mask for preoxygenation,[13] although the other trial did not show a significant difference.[14] International guidelines state that preoxygenation with either noninvasive ventilation or an oxygen mask is acceptable.[15-17] We conducted the Pragmatic Trial Examining Oxygenation Prior to Intubation (PREOXI) trial to determine the effect of preoxygenation with noninvasive ventilation, as compared with preoxygenation with an oxygen mask, on the incidence of hypoxemia during tracheal intubation among critically ill adults. We hypothesized that the incidence would be lower with noninvasive ventilation.

Methods

Trial Design and Oversight

The Pragmatic Critical Care Research Group conducted this pragmatic, multicenter, unblinded, randomized, parallel-group trial in which preoxygenation with noninvasive ventilation was compared with preoxygenation with an oxygen mask for tracheal intubation in critically ill adults. The trial was initiated by the investigators and approved by the institutional review board at Vanderbilt University Medical Center, with secondary concurrence by the Office of Human Research Oversight of the Defense Health Agency.[4] The trial was funded by the U.S. Department of Defense, which had no role in the conception, design, or conduct of the trial; the collection, management, analysis, interpretation, or presentation of the data; or the preparation, review, or approval of the manuscript. The requirement for written informed consent was waived; patients were provided a patient information sheet about the trial after enrollment (details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was registered at ClinicalTrials.gov before initiation and was overseen by an independent data and safety monitoring board. The trial protocol and statistical analysis plan were published before the conclusion of enrollment[18] and are available with the full text of the article at NEJM.org. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Sites and Patient Population

The trial was conducted at 24 sites (7 emergency departments and 17 ICUs) in 15 medical centers in the United States. Critically ill adults (age, ≥18 years) undergoing tracheal intubation that involved the use of sedation and a laryngoscope were eligible. Patients were excluded if they were known to be pregnant, were known to be a prisoner, were already receiving positive-pressure ventilation, had apnea or hypopnea, or had an immediate need for tracheal intubation that precluded randomization. Patients were also excluded if the clinician performing the procedure (referred to as the "operator") determined that preoxygenation with noninvasive ventilation or

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an oxygen mask was either necessary or contraindicated. Details of the trial sites and complete lists of inclusion and exclusion criteria are provided in the Supplementary Appendix.

RANDOMIZATION

Patients were randomly assigned in a 1:1 ratio to receive preoxygenation with either noninvasive ventilation or an oxygen mask. Randomization was performed with the use of permuted blocks of variable size and was stratified according to trial site. Trial-group assignments were placed in sequentially numbered, opaque envelopes and remained concealed until after enrollment. Given the nature of the intervention, clinicians and research personnel were aware of trial-group assignments after randomization.

TRIAL INTERVENTIONS

For the patients in the noninvasive-ventilation group, the operators were instructed to administer noninvasive ventilation using a tight-fitting mask connected to either a conventional mechanical ventilator (a ventilator capable of providing invasive mechanical ventilation) or a dedicated noninvasive ventilator before the induction of anesthesia. The operators selected the type of ventilator and the mode. Best-practice recommendations for preoxygenation with noninvasive ventilation were provided to the operators, who were instructed to administer noninvasive ventilation from the start of preoxygenation until the initiation of laryngoscopy and to set an F_{IO_2} of 100%, an expiratory pressure of at least 5 cm of water, an inspiratory pressure of at least 10 cm of water, and a respiratory rate of at least 10 breaths per minute (see the protocol).

For the patients in the oxygen-mask group, the operators were instructed to administer supplemental oxygen using either a nonrebreather mask or bag-mask device without manual ventilation before the induction of anesthesia; the choice between the two was made by the operators.[19] Best-practice recommendations for preoxygenation with an oxygen mask were provided to the operators, who were instructed to administer supplemental oxygen through the oxygen mask from the start of preoxygenation until the initiation of laryngoscopy and to administer the highest flow rate of oxygen available (≥15 liters per minute).

The patients in both trial groups underwent preoxygenation for at least 3 minutes before the induction of anesthesia (if feasible), as specified in the protocol. The protocol allowed operators to provide, at their discretion, ventilation with a bag-mask device to patients in either trial group after induction of anesthesia (additional details are provided in the Supplementary Appendix). The protocol also allowed for the administration of supplemental oxygen through a standard nasal cannula or high-flow nasal cannula to the patients in either trial group during preoxygenation, during the interval between induction of anesthesia and initiation of laryngoscopy, and during the interval between initiation of laryngoscopy and tracheal intubation.

TRIAL OUTCOMES

The primary outcome was hypoxemia during intubation, defined by an oxygen saturation of less than 85% during the interval between induction of anesthesia and 2 minutes after tracheal intubation. The secondary outcome was the lowest oxygen saturation during the interval between induction of anesthesia and 2 minutes after tracheal intubation. Exploratory outcomes included hemodynamic events that could result from receipt of positive-pressure ventilation or from severe hypoxemia, including hypotension (systolic blood pressure, <65 mm Hg), new or increased use of vasopressors, and cardiac arrest during the interval between induction of anesthesia and 2 minutes after tracheal intubation.

Safety outcomes were designed to assess the clinical, radiographic, and physiological manifestations of oropharyngeal or gastric aspiration during intubation. These outcomes included aspiration during intubation, as reported by the operator; a new infiltrate identified on chest imaging in the 24 hours after induction; and the oxygen saturation and F_{IO_2} at 24 hours after induction. Additional details regarding trial outcomes are provided in the Supplementary Appendix.

DATA COLLECTION

Trained observers who were not involved in the performance of the intubation collected data on the primary and secondary outcomes by recording the oxygen saturation as measured by a pulse

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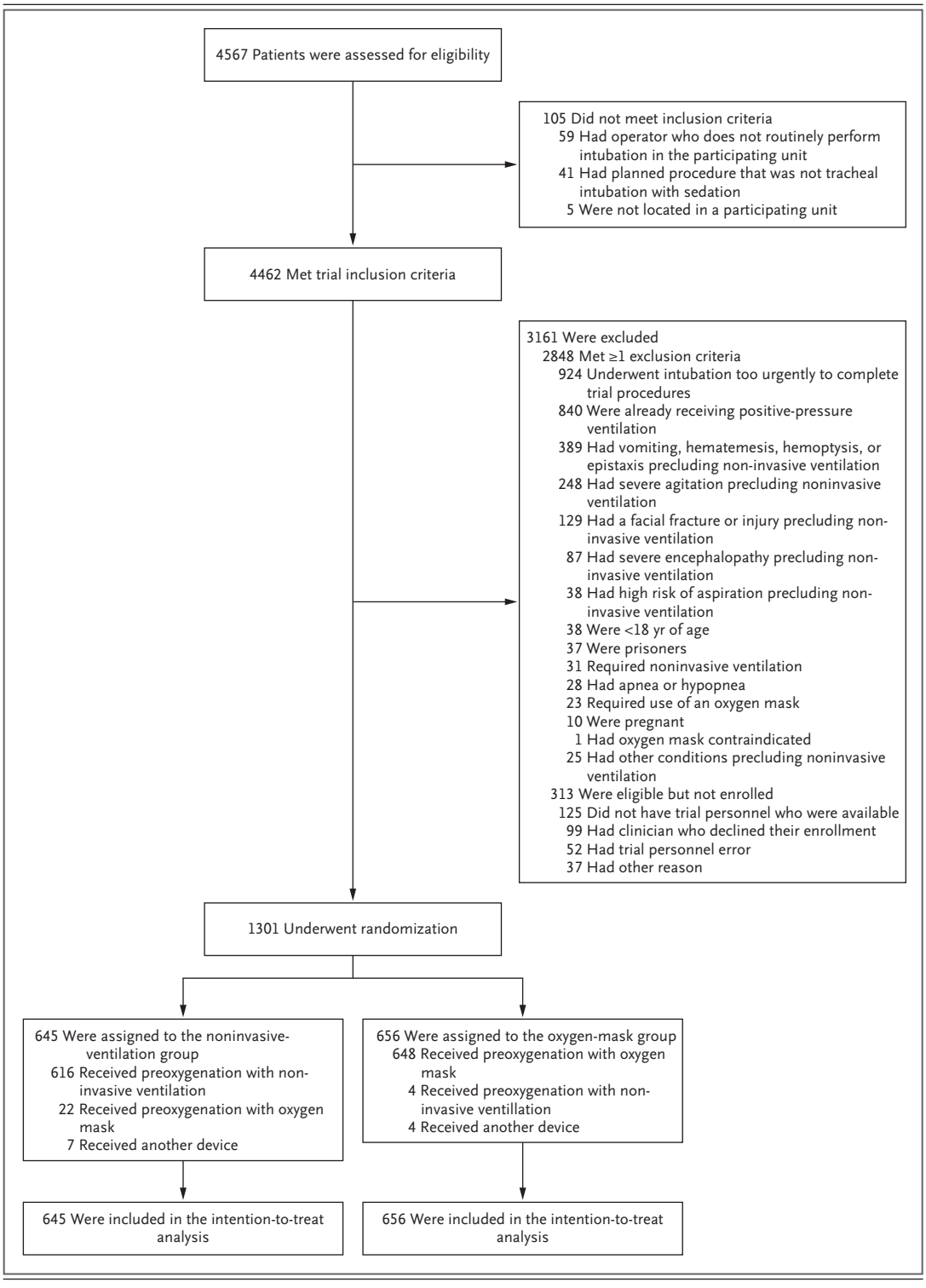

oximeter at the time of induction of anesthesia and the lowest oxygen saturation during the interval between induction of anesthesia and 2 minutes after intubation. The observer also collected data on the number of attempts required for successful intubation, the lowest systolic blood pressure, and the administration of vasopressors during the interval between induction

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Figure 1 (facing page). Screening, Randomization, and Analysis.

A total of 4567 patients underwent screening for eligibility, of whom 3266 were excluded. The most common reasons for exclusion were that the intubation was too urgent to complete trial procedures (20.2% of the patients), the patient was already receiving positive-pressure ventilation (18.4% of the patients), and the patient had vomiting, hematemesis, hemoptysis, or epistaxis (8.5% of the patients). Of the 1301 patients who were enrolled and underwent randomization, 645 were assigned to the noninvasive-ventilation group and 656 were assigned to the oxygen-mask group. All the patients who had undergone randomization were included in the intention-to-treat analysis. Other conditions precluding the use of noninvasive ventilation and other reasons for eligible patients not being enrolled are presented in Table S1 in the Supplementary Appendix.

of anesthesia and 2 minutes after intubation. Immediately after intubation, the operator reported the Cormack–Lehane grade of laryngeal view,[20] the occurrence of oropharyngeal or gastric aspiration, cardiac arrest during the interval between induction of anesthesia and 2 minutes after intubation, and the approximate number of previous intubations the operator had performed. Trial personnel reviewed medical records to collect data on the patients' baseline characteristics, periprocedural care, and clinical outcomes.

STATISTICAL ANALYSIS

Details regarding the determination of the sample size have been reported previously[18] and are provided in the Supplementary Appendix. Assuming an incidence of hypoxemia of 17% in the oxygen-mask group,[21] 85% statistical power, and a two-sided alpha level of 0.05, we calculated that a sample of 1264 patients would be needed to detect an absolute between-group difference of 6 percentage points in the incidence of hypoxemia. To ensure adequate power if data were missing in up to 3% of the patients, we planned to enroll a total of 1300 patients (650 per trial group). A single interim analysis was planned to be performed after 650 patients had been enrolled. A P value threshold of 0.001 or less for the between-group difference in the primary outcome was used as the value that would justify stopping the trial at the time of the interim analysis.

The primary analysis was an unadjusted, intention-to-treat comparison of the primary outcome between the trial groups that was performed with the use of the chi-square test. The primary analysis included all the patients who had undergone randomization, except for those who were missing data on the primary outcome. Secondary analyses of the primary outcome included an adjusted analysis that was performed with the use of a generalized linear mixed-effects model with a random effect for trial site and fixed effects for prespecified baseline covariates. In accordance with published guidelines,[22] we examined whether prespecified baseline variables modified the effect of trial-group assignment on the primary outcome using a logistic-regression model with trial-group assignment, the proposed effect modifier, and the interaction between trial-group assignment and the proposed effect modifier as independent variables. Additional details of these analyses are provided in the Supplementary Appendix.

Between-group differences in secondary and exploratory outcomes are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between the two trial groups. All the statistical analyses were performed with the use of R software, version 4.31 (R Foundation for Statistical Computing).

RESULTS

PATIENTS

Between March 10, 2022, and October 14, 2023, a total of 4567 patients were assessed for eligibility, of whom 1301 were enrolled in the trial. The reasons for exclusion are listed in Figure 1 and Table S1 in the Supplementary Appendix. The median age was 61 years, and 48.1% of the patients had hypoxemic respiratory failure. Tracheal intubation was performed in an ICU in 73.2% of the patients and in an emergency department in 26.8%. In total, 85.9% of the intubations were performed by a resident or a fellow. Operators had performed a median of 50 previous tracheal intubations (Table S2). A total of 645 patients (49.6%) were assigned to the noninvasive-ventilation group, and 656 patients (50.4%) were assigned to the oxygen-mask group (Table 1 and Tables S3 through S6). The representativeness of the patients is described in the Supplementary Appendix.

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Noninvasive Ventilation (N=645)	Oxygen Mask (N=656)
Median age (IQR) — yr	61 (47–71)	61 (47–70)
Female sex — no. (%)	255 (39.5)	260 (39.6)
Race and ethnic group — no. (%)†		
Non-Hispanic White	384 (59.5)	399 (60.8)
Non-Hispanic Black	124 (19.2)	152 (23.2)
Hispanic	80 (12.4)	63 (9.6)
Other	48 (7.4)	36 (5.5)
Not reported	9 (1.4)	6 (0.9)
Median body-mass index (IQR)‡	27.6 (23.3–32.9)	26.6 (22.5–32.4)
Location of intubation — no. (%)		
ICU	476 (73.8)	476 (72.6)
Emergency department	169 (26.2)	180 (27.4)
Chronic conditions — no. (%)§		
Cirrhosis	124 (19.2)	104 (15.9)
Chronic obstructive pulmonary disease	98 (15.2)	81 (12.3)
Congestive heart failure	80 (12.4)	91 (13.9)
Obstructive sleep apnea	45 (7.0)	40 (6.1)
Acute conditions — no. (%)§		
Altered mental status	402 (62.3)	390 (59.5)
Sepsis or septic shock	301 (46.7)	312 (47.6)
Pneumonia	107 (16.6)	102 (15.5)
Gastrointestinal bleeding	107 (16.6)	102 (15.5)
Traumatic injury	40 (6.2)	36 (5.5)
Median APACHE II score (IQR)¶	17 (12–23)	17 (12–23)
Median Glasgow Coma Scale score (IQR)‖	12 (8–15)	12 (8–15)
Treatment or measurement within the hour before enrollment		
Receipt of vasopressors — no. (%)	178 (27.6)	178 (27.1)
Receipt of high-flow nasal cannula — no. (%)**	150 (23.3)	165 (25.2)
Median lowest oxygen saturation (IQR) — %††	95 (92–98)	95 (92–98)
Median highest FIO_2 (IQR)‡‡	0.33 (0.21–0.66)	0.36 (0.21–0.70)
Ratio of oxygen saturation to FIO_2§§		
Median (IQR)	271 (145–426)	268 (124–423)
≤315 — no. (%)	328 (58.9)	331 (59.7)

* FIO_2 denotes fraction of inspired oxygen, ICU intensive care unit, and IQR interquartile range. Percentages may not total 100 because of rounding.

† Race and ethnic group were reported by the patients or their surrogates as part of clinical care and were obtained from the electronic health record by research personnel using fixed categories.

‡ Data on the body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for 12 patients (0.9%) — 5 in the noninvasive-ventilation group and 7 in the oxygen-mask group.

§ Data on chronic and acute conditions were abstracted from the electronic health record and grouped into prespecified categories. Patients could have more than one chronic condition and more than one acute condition.

¶ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating a greater severity of illness.

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Table 1. (Continued.)

‖ Data on the most recent Glasgow Coma Scale score before enrollment were missing for 5 patients (0.4%) — 3 in the noninvasive-ventilation group and 2 in the oxygen-mask group.
** High-flow nasal cannula was defined as a specialized device capable of heating and humidifying gas and delivering gas flows between 30 and 60 liters per minute.
†† Data on the lowest oxygen saturation in the hour before enrollment were missing for 128 patients (9.8%) — 61 in the noninvasive-ventilation group and 67 in the oxygen-mask group.
‡‡ Data on the highest FIO_2 in the hour before enrollment were missing for 184 patients (14.1%) — 86 in the noninvasive-ventilation group and 98 in the oxygen-mask group.
§§ A ratio of oxygen saturation to FIO_2 of 315 or lower was the threshold used to define acute respiratory distress syndrome.[23] Data on this ratio were missing for 190 patients (14.6%) — 88 in the noninvasive-ventilation group and 102 in the oxygen-mask group.

OXYGENATION AND VENTILATION

Of the 645 patients in the noninvasive-ventilation group, 616 (95.5%) received noninvasive ventilation for preoxygenation, and 648 of the 656 patients (98.8%) in the oxygen-mask group received an oxygen mask for preoxygenation. The duration of preoxygenation was at least 3 minutes in 618 of 640 patients (96.6%) in the noninvasive-ventilation group and in 622 of 655 patients (95.0%) in the oxygen-mask group. An oxygen saturation of 95% or less at the time of induction of anesthesia (the end of preoxygenation) was recorded in 52 of 625 patients (8.3%) in the noninvasive-ventilation group and in 112 of 643 patients (17.4%) in the oxygen-mask group (absolute risk difference, −9.1 percentage points; 95% confidence interval [CI], −12.7 to −5.5) (Figs. S1, S2, and S3). Additional characteristics of the tracheal intubation procedure are shown in Table 2 and Tables S7 through S12.

PRIMARY AND SECONDARY OUTCOMES

Hypoxemia during the interval between induction of anesthesia and 2 minutes after intubation (the primary outcome) occurred in 57 of 624 patients (9.1%) in the noninvasive-ventilation group and in 118 of 637 patients (18.5%) in the oxygen-mask group (absolute risk difference, −9.4 percentage points; 95% CI, −13.2 to −5.6; P<0.001) (Table 3 and Figs. S4 and S5); results were similar in the adjusted analyses (Table S13 and S14). The median lowest oxygen saturation during the interval between induction of anesthesia and 2 minutes after tracheal intubation (the secondary outcome) was 99% (interquartile range, 95 to 100) in the noninvasive-ventilation group and 97% (interquartile range, 89 to 100) in the oxygen-mask group (median difference, 2%; 95% CI, 1 to 3).

The results of prespecified subgroup analyses of the primary outcome are shown in Figure 2. The effect of noninvasive ventilation on the incidence of hypoxemia appeared to be greater among patients with a higher body-mass index (Fig. S6). None of the other characteristics appeared to modify the effect of noninvasive ventilation on the incidence of hypoxemia (Figs. S7 through S10).

EXPLORATORY OUTCOMES

During the interval between induction of anesthesia and 2 minutes after tracheal intubation, an oxygen saturation of less than 80% was recorded in 39 of 624 patients (6.2%) in the noninvasive-ventilation group and in 84 of 637 patients (13.2%) in the oxygen-mask group (absolute risk difference, −6.9 percentage points; 95% CI, −10.2 to −3.7). An oxygen saturation of less than 70% was recorded in 15 patients (2.4%) in the noninvasive-ventilation group and in 36 patients (5.7%) in the oxygen-mask group (absolute risk difference, −3.2 percentage points; 95% CI, −5.4 to −1.1). Cardiac arrest during the interval between induction of anesthesia and 2 minutes after tracheal intubation occurred in 1 of 645 patients (0.2%) in the noninvasive-ventilation group and in 7 of 656 patients (1.1%) in the oxygen-mask group (absolute risk difference, −0.9 percentage points; 95% CI, −1.8 to −0.1).

SAFETY OUTCOMES

Aspiration occurred in 6 of 645 patients (0.9%) in the noninvasive-ventilation group and in 9 of 656 patients (1.4%) in the oxygen-mask group (absolute risk difference, −0.4 percentage points; 95% CI, −1.6 to 0.7) (Table S15). The incidence of new opacity on chest radiography and of pneumothorax was similar in the two trial groups. The oxygen saturation and FIO_2 at 24 hours after intubation were also similar in the two trial groups (Table 3).

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Table 2. Characteristics of the Intubation Procedure.

Characteristic	Noninvasive Ventilation (N=645)	Oxygen Mask (N=656)	Difference (95% CI)*
Before induction of anesthesia			
Preoxygenation method — no./total no. (%)†			
Noninvasive ventilation	616/645 (95.5)	4/656 (0.6)	—
Oxygen mask	22/645 (3.4)	648/656 (98.8)	—
Other	7/645 (1.1)	4/656 (0.6)	—
Duration of preoxygenation ≥3 min — no./total no. (%)	618/640 (96.6)	622/655 (95.0)	1.6 (–0.6 to 3.8)
Lowest oxygen saturation during preoxygenation — no./total no. (%)			
>95%	494/627 (78.8)	456/631 (72.3)	6.5 (1.8 to 11.3)
91–95%	70/627 (11.2)	98/631 (15.5)	–4.4 (–8.1 to –0.6)
≤90%	63/627 (10.0)	77/631 (12.2)	–2.2 (–5.6 to 1.3)
At the time of induction			
Oxygen saturation‡			
Median (IQR) — %	100 (99 to 100)	100 (97 to 100)	0 (0 to 1)
Distribution — no./total no. (%)			
>95%	573/625 (91.7)	531/643 (82.6)	9.1 (5.5 to 12.7)
91–95%	29/625 (4.6)	70/643 (10.9)	–6.2 (–9.2 to –3.3)
≤90%	23/625 (3.7)	42/643 (6.5)	–2.9 (–5.3 to –0.4)
Median systolic blood pressure (IQR)§	124 (107 to 143)	129 (111 to 148)	–5 (–10 to –1)
Sedative administered — no./total no. (%)	644/645 (99.8)	653/655 (99.7)	0.2 (–0.4 to 0.7)
Neuromuscular blocking medication administered — no./total no. (%)	636/644 (98.8)	639/653 (97.9)	0.9 (–0.5 to 2.3)
During the interval between induction and initiation of laryngoscopy			
Supplemental oxygen administered — no./total no. (%)	603/639 (94.4)	625/655 (95.4)	–1.1 (–3.5 to 1.3)
Positive-pressure ventilation administered — no./total no. (%)¶	563/639 (88.1)	204/655 (31.1)	57.0 (52.6 to 61.3)
Type of positive-pressure ventilation administered — no./total no. (%)			
Noninvasive ventilation	513/639 (80.3)	2/655 (0.3)	80.0 (76.9 to 83.1)
Bag-mask ventilation	57/639 (8.9)	202/655 (30.8)	–21.9 (–26.1 to –17.7)

* The difference is reported in percentage points for categorical variables, and the difference in the median value is reported for continuous variables.
† Method of preoxygenation is presented in three mutually exclusive categories: patients who received noninvasive ventilation, patients who received an oxygen mask and did not receive noninvasive ventilation, and patients who received another method of preoxygenation (e.g., nasal cannula) and did not receive noninvasive ventilation or an oxygen mask. Additional details of devices used during preoxygenation are provided in Table S7 in the Supplementary Appendix.
‡ Data on oxygen saturation at the time of induction of anesthesia were missing for 33 patients (2.5%) — 20 in the noninvasive-ventilation group and 13 in the oxygen-mask group.
§ Data on systolic blood pressure at the time of induction of anesthesia were missing for 50 patients (3.8%) — 26 in the noninvasive-ventilation group and 24 in the oxygen-mask group.
¶ Positive-pressure ventilation includes noninvasive ventilation and bag-mask ventilation. Patients could receive both.

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Table 3. Outcomes of Tracheal Intubation.

Outcome	Noninvasive Ventilation (N=645)	Oxygen Mask (N=656)	Difference (95% CI)*
Primary outcome			
Hypoxemia during intubation — no./total no. (%)†‡	57/624 (9.1)	118/637 (18.5)	−9.4 (−13.2 to −5.6)§
Secondary outcome			
Median lowest oxygen saturation (IQR) — %‡	99 (95 to 100)	97 (89 to 100)	2 (1 to 3)
Exploratory procedural outcomes			
Lowest oxygen saturation <80% — no./total no. (%)‡	39/624 (6.2)	84/637 (13.2)	−6.9 (−10.2 to −3.7)
Lowest oxygen saturation <70% — no./total no. (%)‡	15/624 (2.4)	36/637 (5.7)	−3.2 (−5.4 to −1.1)
Cardiovascular collapse — no./total no. (%)¶	113/645 (17.5)	127/656 (19.4)	−1.8 (−6.1 to 2.4)
Systolic blood pressure <65 mm Hg — no./total no. (%)	18/621 (2.9)	28/633 (4.4)	−1.5 (−3.6 to 0.6)
New or increased use of vasopressors — no./total no. (%)	111/645 (17.2)	117/656 (17.8)	−0.6 (−4.8 to 3.5)
Cardiac arrest — no./total no. (%)‖	1/645 (0.2)	7/656 (1.1)	−0.9 (−1.8 to −0.1)
Successful intubation on the first attempt — no./total no. (%)	534/645 (82.8)	535/656 (81.6)	1.2 (−2.9 to 5.4)
Median time from induction to intubation (IQR) — seconds	115 (89 to 150)	113 (85 to 152)	2 (−5 to 9)
Exploratory safety outcomes			
Operator-reported aspiration — no./total no. (%)**	6/645 (0.9)	9/656 (1.4)	−0.4 (−1.6 to 0.7)
New infiltrate on chest imaging — no./total no. (%)††	144/509 (28.3)	148/497 (29.8)	−1.5 (−7.1 to 4.1)
New pneumothorax — no./total no. (%)‡‡	7/509 (1.4)	7/497 (1.4)	0.0 (−1.5 to 1.4)
Median oxygen saturation at 24 hr (IQR)§§	97 (95 to 100)	97 (95 to 100)	0 (−1 to 1)
Median F_{IO_2} at 24 hr (IQR)¶¶	0.40 (0.30 to 0.40)	0.40 (0.30 to 0.40)	0.01 (−0.05 to 0.05)
Exploratory clinical outcomes‖‖			
Median ventilator-free days (IQR)	21 (0 to 26)	17 (0 to 25)	4 (−1 to 9)
Median ICU-free days (IQR)	16 (0 to 23)	14 (0 to 23)	2 (−1 to 8)
In-hospital death — no./total no. (%)	209/645 (32.4)	217/656 (33.1)	−0.7 (−5.8 to 4.4)

* The difference is reported in percentage points for categorical variables, and the difference in the median value is reported for continuous or ordinal variables.

† Hypoxemia was defined by an oxygen saturation of less than 85%, as measured by pulse oximetry, during the interval between induction and 2 minutes after tracheal intubation.

‡ Data on the oxygen saturation during the interval between induction of anesthesia and 2 minutes after intubation were missing for 40 patients (3.1%) — 21 in the noninvasive-ventilation group and 19 in the oxygen-mask group. Data were unavailable because of inadequate plethysmographic waveform for 17 patients in each trial group and because of a data-collection error for 4 patients in the noninvasive-ventilation group and for 2 patients in the oxygen-mask group.

§ $P<0.001$.

¶ Cardiovascular collapse was defined as the occurrence of a systolic blood pressure lower than 65 mm Hg, new or increased use of vasopressors, or cardiac arrest during the interval between induction of anesthesia and 2 minutes after tracheal intubation.

‖ Of the 8 patients who had a cardiac arrest during the interval between induction and 2 minutes after tracheal intubation, 4 died within 1 hour — 1 in the noninvasive-ventilation group and 3 in the oxygen-mask group.

** Operator-reported aspiration was recorded by the operator on a standardized case-report form immediately after completion of the intubation procedure.

†† A new infiltrate on chest imaging was defined as the presence of new air bronchograms, centrilobular nodules, consolidation, ground-glass opacity, infiltrate, opacity, parenchymal opacification, pneumonia, pneumonitis pulmonary edema, or a tree-in-bud pattern, as reported in the clinical interpretation of chest imaging obtained in the 24 hours after enrollment.

‡‡ New pneumothorax was defined as a radiology report of a new pneumothorax on chest imaging in the 24 hours after enrollment.

§§ Data on the oxygen saturation at 24 hours were missing for 118 patients (9.1%) — 56 in the noninvasive-ventilation group and 62 in the oxygen-mask group.

¶¶ Data on the F_{IO_2} at 24 hours were missing for 117 patients (9.0%) — 55 in the noninvasive-ventilation group and 62 in the oxygen-mask group.

‖‖ Ventilator-free days, ICU-free days, and in-hospital death were assessed at 28 days, with follow-up data censored at the time of hospital discharge.

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DISCUSSION

In this multicenter, randomized trial involving critically ill adults undergoing tracheal intubation, the incidence of hypoxemia was lower by 9.4 percentage points among those who received preoxygenation with noninvasive ventilation than among those who received preoxygenation with an oxygen mask. Preoxygenation with noninvasive ventilation did not appear to increase the incidence of aspiration. These findings have important clinical implications because hypoxemia during intubation is associated with cardiac arrest and death,[5,24,25] and in current clinical care worldwide, most critically ill adults receive preoxygenation with an oxygen mask rather than with noninvasive ventilation.[3,4]

The effects of preoxygenation with noninvasive ventilation as compared with an oxygen mask in critically ill adults undergoing tracheal intubation have been examined previously in two small randomized trials.[13,14] These trials focused on a narrow population of patients with acute hypoxemic respiratory failure undergoing tracheal intubation in an ICU, included fewer than 300 patients (combined), and showed inconclusive results. In contrast, our trial involving 1301 critically ill adults with a broad range of medical conditions undergoing tracheal intubation in a variety of clinical settings showed that preoxygenation with noninvasive ventilation decreased the risk of hypoxemia during tracheal intubation by approximately half. The results appeared to be consistent among prespecified subgroups, including among patients breathing ambient air without supplemental oxygen in the hour before intubation. Cardiac arrest during intubation occurred in 1 patient (0.2%) in the

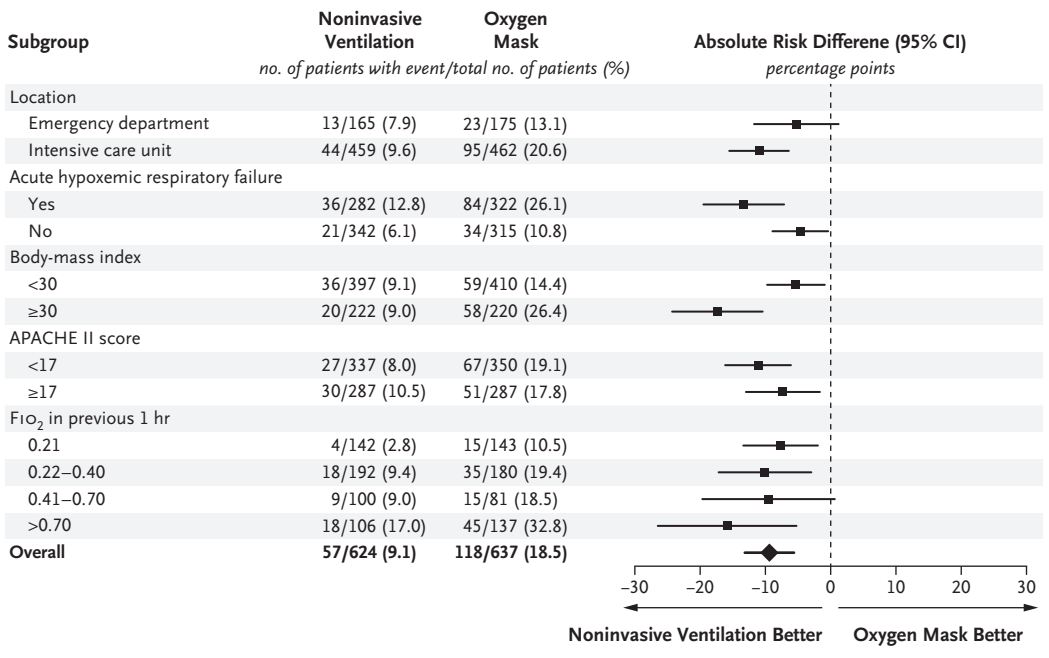

Figure 2. Subgroup Analyses of the Risk of Hypoxemia during Intubation.

Shown are the absolute risk differences and 95% confidence intervals for the primary outcome (hypoxemia during intubation, defined by an oxygen saturation of <85% during the interval between induction of anesthesia and 2 minutes after tracheal intubation) in prespecified subgroups. Absolute risk differences in the noninvasive-ventilation group as compared with the oxygen-mask group were calculated with the use of a logistic-regression model with independent variables of trial group, the proposed effect modifier, and the interaction between the trial group and the proposed effect modifier. Absolute risk differences of less than 0 indicate a lower likelihood of hypoxemia with the use of noninvasive ventilation for preoxygenation. The body-mass index is the weight in kilograms divided by the square of the height in meters. Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating a greater severity of illness. FIO_2 denotes fraction of inspired oxygen.

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noninvasive-ventilation group and in 7 patients (1.1%) in the oxygen-mask group (absolute risk difference, −0.9 percentage points; 95% CI, −1.8 to −0.1). Although the small number of events precludes firm conclusions, this finding may suggest that, by preventing hypoxemia during intubation, preoxygenation with noninvasive ventilation could potentially reduce the incidence of downstream outcomes such as cardiac arrest and death.

A commonly cited reason for avoiding preoxygenation with noninvasive ventilation is a hypothesized risk of aspiration due to positive-pressure ventilation.[26-28] In our trial, noninvasive ventilation did not appear to affect the incidence of aspiration during the procedure, the incidence of a new opacity on chest radiography after the procedure, or oxygen saturation and F_{IO_2} in the patients at 24 hours, findings that are consistent with the results of previous trials of preoxygenation with noninvasive ventilation[13,14] and of positive-pressure ventilation after induction of anesthesia.[29] Additional potential barriers to preoxygenation with noninvasive ventilation could include the availability of the equipment or the time required to set it up. In our pragmatic trial, preoxygenation with noninvasive ventilation was delivered by treating clinicians using the equipment available in clinical care, without involvement by research personnel. Because many conventional mechanical ventilators can provide noninvasive ventilation, preoxygenation with noninvasive ventilation frequently can be provided with the use of the same equipment required for mechanical ventilation after intubation. Approximately 20% of the patients who underwent screening for eligibility in this trial were excluded because the urgency of the intubation precluded the performance of the trial procedures, as compared with 11 to 18% of the patients who were excluded because of urgency in previous trials of airway management evaluating interventions that required no additional time to set up.[4,7,29] The similar percentages of exclusions for urgency between this trial and previous trials of emergency tracheal intubation suggest that, for most patients undergoing tracheal intubation in an emergency department or ICU, preoxygenation with noninvasive ventilation is logistically feasible.

Our trial has several strengths. Enrollment of a large sample of patients provided sufficient statistical power to detect clinically meaningful differences in the incidence of hypoxemia between the trial groups; conduct of the trial in emergency departments and ICUs at multiple sites and enrollment of critically ill adults with a broad range of conditions increased the generalizability of the findings; and collection of outcome data by an independent observer minimized observer bias.

Our trial also has several limitations. Because patients who were already receiving positive-pressure ventilation at the time of eligibility assessment were excluded, the results of our trial do not inform decisions regarding preoxygenation in this patient population. Among the patients who underwent screening in the trial, 389 (8.5%) were excluded because they had vomiting, hematemesis, hemoptysis, or epistaxis, and 38 (0.8%) were excluded because clinicians otherwise perceived them to be at very high risk for aspiration; our results do not inform the safety or effectiveness of noninvasive ventilation in such patients. Our trial did not evaluate the use of high-flow nasal cannula during tracheal intubation and cannot inform its effectiveness, either alone or in combination with an oxygen mask. However, the benefit of noninvasive ventilation observed in the current trial was of similar magnitude to that observed in a previous trial comparing noninvasive ventilation with high-flow nasal cannula.[30] Finally, patients, clinicians, and trial personnel were aware of the trial-group assignments.

In this trial involving critically ill adults undergoing tracheal intubation in an emergency department or an ICU, the incidence of hypoxemia was lower with preoxygenation with noninvasive ventilation than with an oxygen mask.

The views expressed are those of the authors and do not necessarily reflect the official views or policy of the U.S. Department of Defense or its components. The informed consent of the patients who participated in this trial was addressed as required by 32 CFR 219 and DODI 3216.02_AFI 40-402 with the use of a patient information sheet, and the institutional review board requirement for written informed consent was waived.

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APPENDIX

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