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Effect of High-Intensity vs Low-Intensity Noninvasive Positive Pressure Ventilation on the Need for Endotracheal Intubation in Patients With an Acute Exacerbation of Chronic Obstructive Pulmonary Disease
The HAPPEN Randomized Clinical Trial

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IMPORTANCE The effect of high-intensity noninvasive positive pressure ventilation (NPPV) on the need for endotracheal intubation in patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) is unknown.

OBJECTIVE To determine whether the use of high-intensity NPPV vs low-intensity NPPV reduces the need for endotracheal intubation in patients with an acute exacerbation of COPD and hypercapnia.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at 30 general respiratory non–intensive care unit wards of Chinese hospitals from January 3, 2019, to January 31, 2022; the last 90-day follow-up was on April 22, 2022. The included patients had an acute exacerbation of COPD and a $Paco_2$ level greater than 45 mm Hg after receiving 6 hours of low-intensity NPPV.

INTERVENTIONS Patients were randomized 1:1 to receive high-intensity NPPV with inspiratory positive airway pressure that was adjusted to obtain a tidal volume 10 mL/kg to 15 mL/kg of predicted body weight (n = 147) or to continue receiving low-intensity NPPV with inspiratory positive airway pressure that was adjusted to obtain a tidal volume of 6 mL/kg to 10 mL/kg of predicted body weight (n = 153). Patients in the low-intensity NPPV group who met the prespecified criteria for the need for endotracheal intubation were allowed to crossover to high-intensity NPPV.

MAIN OUTCOMES AND MEASURES The primary outcome was the need for endotracheal intubation during hospitalization, which was defined by prespecified criteria. There were 15 prespecified secondary outcomes, including endotracheal intubation.

RESULTS The trial was terminated by the data and safety monitoring board and the trial steering committee after an interim analysis of the first 300 patients. Among the 300 patients who completed the trial (mean age, 73 years [SD, 10 years]; 68% were men), all were included in the analysis. The primary outcome of meeting prespecified criteria for the need for endotracheal intubation occurred in 7 of 147 patients (4.8%) in the high-intensity NPPV group vs 21 of 153 (13.7%) in the low-intensity NPPV group (absolute difference, −9.0% [95% CI, −15.4% to −2.5%], 1-sided P = .004). However, rates of endotracheal intubation did not significantly differ between groups (3.4% [5/147] in the high-intensity NPPV group vs 3.9% [6/153] in the low-intensity NPPV group; absolute difference, −0.5% [95% CI, −4.8% to 3.7%], P = .81). Abdominal distension occurred more frequently in the high-intensity NPPV group (37.4% [55/147]) compared with the low-intensity NPPV group (25.5% [39/153]).

CONCLUSIONS AND RELEVANCE Patients with COPD and persistent hypercapnia in the high-intensity NPPV group (vs patients in the low-intensity NPPV group) were significantly less likely to meet criteria for the need for endotracheal intubation; however, patients in the low-intensity NPPV group were allowed to crossover to high-intensity NPPV, and the between-group rate of endotracheal intubation was not significantly different.

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Visual Abstract

Editorial

Supplemental content

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Group Information: A list of the HAPPEN Investigators appears in Supplement 4.

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Noninvasive positive pressure ventilation (NPPV) has been increasingly used for patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD).[1,2] Strong evidence indicates that NPPV is associated with reduced rates of endotracheal intubation and hospital mortality compared with standard oxygen therapy.[3-5] Low-intensity NPPV, which uses a relatively low inspiratory positive airway pressure (IPAP; typically <18 cm H_2O), is commonly used in clinical practice.[6,7] Approximately 15% of patients with an acute exacerbation of COPD need endotracheal intubation when receiving NPPV,[2,3,7,8] which may be partly associated with inadequate pressure support and limited improvement in alveolar ventilation with the use of low-intensity NPPV.[3,7,9,10]

High-intensity NPPV, a form of pressure-limited ventilation (IPAP levels typically range from 20-30 cm H_2O), was introduced as a novel ventilatory approach to maximally decrease elevated levels of $Paco_2$ toward normocapnia with stepwise uptitration of IPAP.[6,11-13] In theory, high-intensity NPPV may be more effective than low-intensity NPPV at augmenting alveolar ventilation and offsetting the extra dead space caused by the face mask and may better reduce inspiratory effort and alleviate dyspnea. In patients with stable COPD and hypercapnia, high-intensity NPPV has been shown to be superior to low-intensity NPPV at reducing inspiratory effort and at improving gas exchange, ventilatory function, lung volume, patient tolerance, and health-related quality of life.[14-16] The addition of high-intensity NPPV to home oxygen therapy may improve the 1-year overall survival of patients with COPD and hypercapnia and may prolong the time to hospital readmission or death within 12 months compared with home oxygen therapy alone.[17,18]

In patients with an acute exacerbation of COPD, our prior trial[19] investigating the physiological effects of NPPV found that high-intensity NPPV was more effective than low-intensity NPPV at decreasing elevated levels of $Paco_2$, reducing inspiratory effort, and alleviating dyspnea. However, the effect of high-intensity NPPV on the need for endotracheal intubation remains unclear in patients with an acute exacerbation of COPD. This multicenter, randomized clinical trial was conducted to determine whether high-intensity NPPV, compared with low-intensity NPPV, could reduce the need for endotracheal intubation during hospitalization in patients with an acute exacerbation of COPD and hypercapnia.

Key Points

Question In patients with an acute exacerbation of chronic obstructive pulmonary disease and hypercapnia who first received 6 hours of low-intensity noninvasive positive pressure ventilation (NPPV), does high-intensity NPPV decrease the likelihood of meeting prespecified criteria for the need for endotracheal intubation compared with continuing low-intensity NPPV?

Findings In this randomized clinical trial involving 300 patients, 4.8% of patients randomized to high-intensity NPPV met prespecified criteria for the need for endotracheal intubation vs 13.7% randomized to low-intensity NPPV, which is a significant difference. However, the rates of endotracheal intubation did not differ significantly between the high-intensity NPPV group (3.4%) and the low-intensity NPPV group (3.9%).

Meaning Patients with an acute exacerbation of chronic obstructive pulmonary disease and persistent hypercapnia were significantly less likely to meet criteria for the need for endotracheal intubation when randomized to high-intensity vs low-intensity NPPV, although patients in the low-intensity NPPV group were allowed to crossover to high-intensity NPPV and the endotracheal intubation rate did not significantly differ between groups.

Methods

Trial Design and Oversight

The HAPPEN (High-intensity vs Low-intensity Noninvasive Positive Pressure Ventilation in an AECOPD) trial was an investigator-initiated, 2-group, single-blind, multicenter, randomized clinical trial conducted in 30 general respiratory non-intensive care unit (ICU) wards from hospitals across China. The trial was conducted between January 3, 2019, and January 31, 2022; the last 90-day follow-up occurred on April 22, 2022. The trial protocol was published before enrollment of the first patient[20] and appears in Supplement 1. The statistical analysis plan appears in Supplement 2. Additional information appears in the eMethods in Supplement 3.

The trial was designed by a steering committee and was approved by the ethics committee at the coordinating center (Beijing Chao-Yang Hospital; approval No. 2018-KE-319) and thereafter by the local ethical committees of all participating centers. The trial adhered to the Good Clinical Practice guidelines, local regulations, and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients, their next of kin, or another surrogate decision-maker as appropriate.

The steering committee oversaw the trial. At each center, a dedicated investigative team (under the leadership of a senior physician) performed daily patient screening, trial enrollment, oversight of protocol adherence, and completion of the case report form. This team comprised 5 or 6 physicians (including 3 senior clinicians) and 5 or 6 respiratory nurses (or respiratory therapists if available). All individuals on the team had extensive experience in the use of NPPV and all underwent standardized protocol training. The administration of NPPV was conducted by physicians or respiratory therapists, with monitoring and documentation carried out by respiratory therapists or nurses. The trial followed the CONSORT (Consolidated Standards of Reporting Trials) guideline.

Participants

Consecutive patients with COPD admitted to 30 general respiratory non-ICU wards were screened for eligibility based on the 2019 diagnostic criteria from the Global Initiative for Chronic Obstructive Lung Disease.[21] Eligible patients met the following criteria: had an arterial pH level of less than 7.35, had a $Paco_2$ level greater than 45 mm Hg at screening entry, and had a persistently elevated level of $Paco_2$ that was greater than 45 mm Hg after receiving low-intensity NPPV for 6 hours.

The exclusion criteria were being younger than 18 years of age; having excessive respiratory secretions or an upper airway obstruction; having undergone a recent oral, facial, or cranial trauma or surgery; having undergone a recent gastric or esophageal surgery; having restrictive ventilatory dysfunction; having active bleeding in the upper gastrointestinal tract; having undergone a recent cardiac or respiratory arrest; having a ratio of Pa_{O_2} to fraction of inspired oxygen (F_{IO_2}) of less than 100 mm Hg; having pneumothorax; having emphysematous bullae that was confirmed by a computed tomographic scan; having ventricular arrhythmia or myocardial ischemia; having severe hemodynamic instability (mean arterial pressure <65 mm Hg); having severe metabolic acidosis (pH level <7.20 and bicarbonate level <22 mmol/L); refusing to receive NPPV or give informed consent; having received prior endotracheal intubation or having undergone a tracheostomy during the current hospitalization; or having a do-not-intubate order (**Figure 1**). Further details appear in Supplement 1 and in the eMethods in Supplement 3.

Randomization and Blinding

Eligible patients were randomized in a 1:1 ratio to receive either high-intensity or low-intensity NPPV. Randomization was conducted using centralized, computer-generated sequences. The allocation sequence was concealed using numbered, opaque, and sealed envelopes. Independent personnel who were not involved in the trial managed the randomization process. Investigators at participating centers had to contact the coordinating center for randomization assignment within the first hour after validating eligibility.

The intervention was not blinded for the investigators or attending physicians. Two independent investigators (one for the intervention and another for the data collection) conducted the study. The data analysis was performed by a statistician who was not involved in the trial. Personnel at the coordinating center and the investigators remained unaware of the study outcomes until data locking occurred in April 2022.

Interventions

In the high-intensity NPPV group, the IPAP level was initially adjusted in increments or decrements of 1 cm H_2O to 2 cm H_2O to obtain a tidal volume of 10 mL/kg to 15 mL/kg of predicted body weight, typically 20 cm H_2O to 30 cm H_2O (or a tolerated maximum), and a respiratory rate of less than 25 breaths/min. Subsequent adjustments to the IPAP were based on arterial blood gas levels (≤30 cm H_2O) to achieve normocapnia if possible or to a decrease in Pa_{CO_2} level toward normocapnia if normocapnia could not be achieved. If the Pa_{CO_2} level was less than 35 mm Hg, the IPAP was reduced to achieve normocapnia.

In the low-intensity NPPV group, the IPAP was initially adjusted in increments or decrements of 1 cm H_2O to 2 cm H_2O to a maximum of 20 cm H_2O, according to the tolerance levels of patients to obtain a tidal volume of 6 mL/kg to 10 mL/kg of predicted body weight and a respiratory rate of less than 25 breaths/min. Subsequent adjustments to the IPAP were based on arterial blood gas levels (≤20 cm H_2O) to achieve a pH level of 7.35 or higher and to reduce Pa_{CO_2} to a level deemed appropriate by the attending physician. Patients were encouraged to use NPPV continuously during the first 6 hours after randomization (brief disconnection was allowed for clearing secretions, drinking, or eating) and for at least 10 hours per day. Further details of NPPV implementation and regarding the devices used appear in Supplement 1 and in eTable 1 in Supplement 3.

The IPAP level and the daily use of NPPV were gradually decreased when the target arterial blood gas levels were reached and clinical conditions improved. Improvement in the clinical condition was defined as the resolution of the acute exacerbation of COPD (confirmed by the attending physician), a respiratory rate of less than 25 breaths/min, a heart rate of less than 110 beats/min, and a Pa_{O_2} level greater than 60 mm Hg with an F_{IO_2} level of less than 0.4.

In the high-intensity NPPV group, the procedures for decreasing the IPAP level were as follows: (1) the IPAP level was decreased by 1 cm H_2O to 2 cm H_2O (ensuring that tidal volume decreased by ≤5% and heart rate and respiratory rate increased by ≤5%); (2) specific arterial blood gas levels were obtained within 2 hours after decreasing the IPAP level, and the IPAP level was returned to the original level if the Pa_{CO_2} level increased by more than 5%; and (3) the IPAP level was allowed to be further decreased over an interval of more than 4 hours, with a total decrease in IPAP level of no more than 4 cm H_2O per day. In low-intensity NPPV group, the procedures for decreasing IPAP were performed at the discretion of the attending physician. In both groups, daily use of NPPV was reduced gradually by no more than 4 hours per day. Daytime NPPV use was shortened first, and then nighttime use was reduced once daytime use was stopped. Use of NPPV was discontinued if it was less than 6 hours per day.

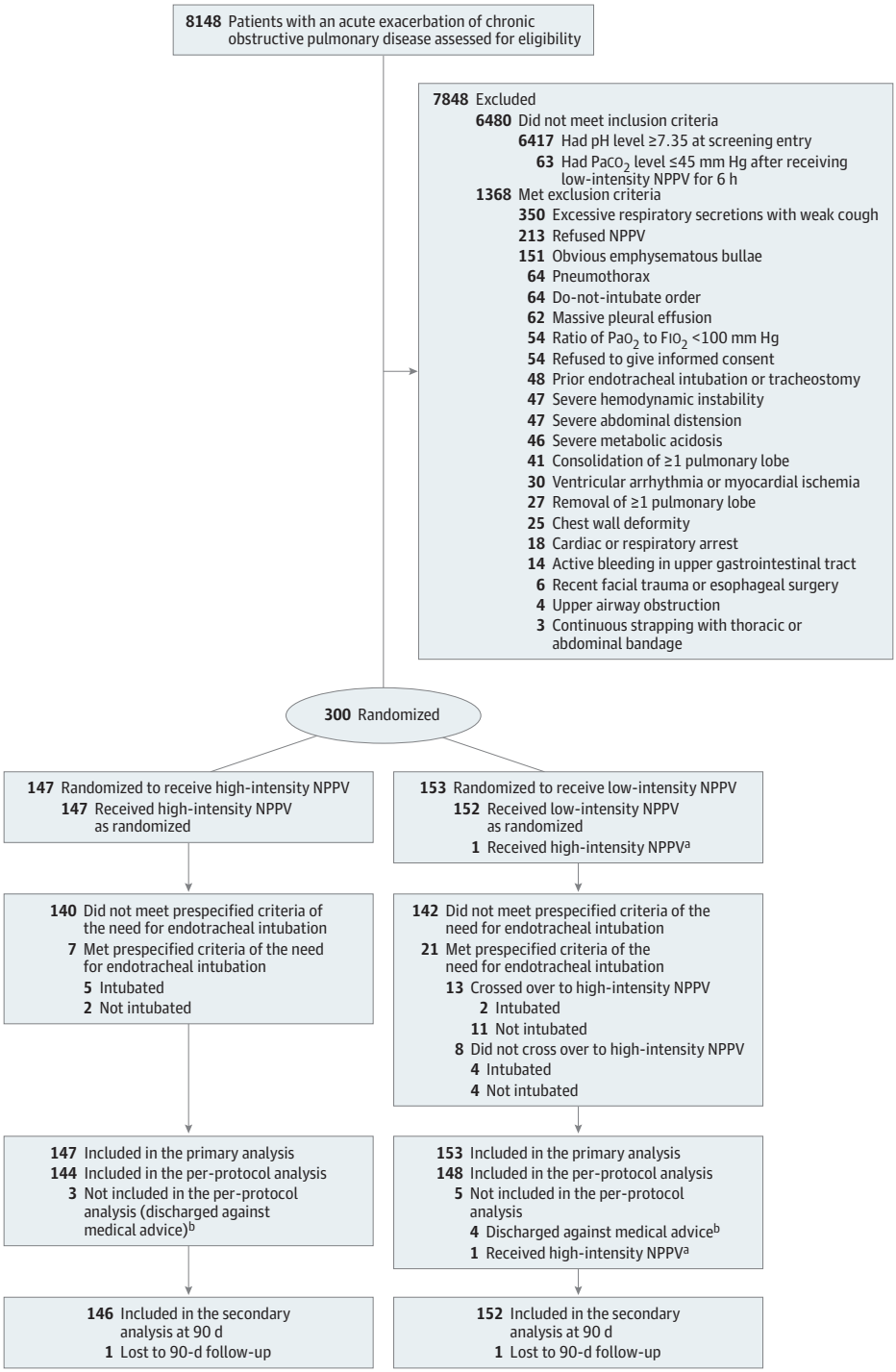
The use of NPPV was resumed if respiratory distress developed within 72 hours of discontinuation. In the high-intensity NPPV group, use of NPPV was also resumed if the Pa_{CO_2} level increased by 10% more than the Pa_{CO_2} level at discontinuation of NPPV. Endotracheal intubation was considered if the prespecified criteria were met. Patients in the low-intensity NPPV group who met the prespecified criteria for endotracheal intubation were allowed to crossover to high-intensity NPPV. Further details of NPPV weaning and endotracheal intubation appear in Supplement 1 and in the eMethods in Supplement 3.

All decisions on medical treatments other than the use of NPPV were based on the 2019 Global Initiative for Chronic Obstructive Lung Disease[21] and routine clinical practice at each center. Patient monitoring routinely included measurements of noninvasive blood pressure, heart rate, pulse oximetry, and electrocardiography.

Outcomes

The primary outcome was the need for endotracheal intubation during hospitalization, which was defined by the prespecified criteria of (1) arterial pH level of less than 7.25 with a Pa_{CO_2} level that increased by more than 20% compared with the baseline level or Pa_{O_2}:F_{IO_2} of less than 100 mm Hg; and (2) the presence of at least 1 of the following: clinical signs suggestive of severely decreased consciousness (eg, coma,

Figure 1. Flow of Patients Through the HAPPEN Trial



FIO_2 indicates fraction of inspired oxygen; HAPPEN, High-intensity vs Low-intensity Noninvasive Positive Pressure Ventilation in an AECOPD; NPPV, noninvasive positive pressure ventilation.

[a]One patient randomized to the low-intensity NPPV group received high-intensity NPPV because of a major protocol violation by the investigators. This patient was included in low-intensity NPPV group for the primary analysis, but not for the per-protocol analysis.

[b]Even though hospital discharge was granted, the data for these patients were included in the primary analysis but not in the per-protocol analysis.

delirium), use of accessory respiratory muscles or thoracoabdominal paradoxical movement, excessive respiratory secretions, aspiration or vomiting, bleeding in upper gastrointestinal tract, severe hemodynamic instability without response to fluid resuscitation and low-dose vasoactive agents, or ventricular or supraventricular arrhythmias; or (3) cardiac or respiratory arrest. Daily assessment of the need for endotracheal intubation was performed. Two independent experts who were blinded to the intervention confirmed the need for endotracheal intubation based on these criteria. In cases of disagreement, a third expert helped make the final decision.

There were 15 prespecified secondary outcomes, including endotracheal intubation during hospitalization, the need for endotracheal intubation and undergoing endotracheal

intubation by day 28, the composite of endotracheal intubation or avoiding endotracheal intubation by crossover to high-intensity NPPV, NPPV weaning success (persistent disconnection of NPPV without respiratory distress within 72 hours), mortality (in hospital, at day 28, and at day 90), ICU admission, discharge from the hospital, length of hospital stay, length of hospital stay after randomization, the number of invasive ventilator-free days (ie, days alive without endotracheal intubation or invasive mechanical ventilation) and ICU-free days (ie, days alive without admission in the ICU) at day 28, and hospital readmission at day 90.

The safety outcomes included the following complications related to NPPV: severe intolerance of NPPV, severe air leakage (unintentional air leakage volume >25 L/min), abdominal distension, NPPV intolerance due to abdominal distension, nasal or oral dryness, inability to remove respiratory secretions, nasal or facial skin necrosis, conjunctivitis, sinus or ear pain, aspiration, hypotension, pneumothorax, acute respiratory distress syndrome, and claustrophobia. Serious adverse events included nosocomial pneumonia, septic shock, multiple organ failure, acute myocardial infarction, life-threatening ventricular arrhythmias, cardiac arrest, cardiogenic shock, gastrointestinal tract bleeding, disseminated intravascular coagulation, pulmonary embolism, and severe alkalosis. The detailed definitions for the outcomes appear in Supplement 1 and in the eMethods in Supplement 3.

Statistical Analysis

The calculation of the sample size was based on our primary hypothesis that the use of high-intensity NPPV would result in a lower need for endotracheal intubation in patients with an acute exacerbation of COPD and persistent hypercapnia compared with low-intensity NPPV. Our previous clinical experience and previous studies[2,3] led us to anticipate a need for endotracheal intubation of 15% in the low-intensity NPPV group. Assuming that the need for endotracheal intubation could be reduced to 6% in the high-intensity NPPV group, we estimated that a minimum sample size of 480 patients would be required. This calculation considered detecting a between-group difference of 9% for the need for endotracheal intubation, with a superiority margin of 2%, 80% power, and a 1-sided α level of .05 using superiority tests for comparing 2 proportions. To account for a dropout rate of 20%, it was determined that enrolling 600 patients would be necessary.

The independent data and safety monitoring board, which had access to the unblinded data during the interim analysis, conducted a single interim analysis after the first 300 patients completed the primary outcome evaluations. The *P* value threshold was .0088 for the interim analysis and .0498 for the final analysis using the O'Brien-Fleming α spending function. The trial could be stopped early if the need for endotracheal intubation differed significantly between groups in the interim analysis. After the interim analysis, we opted to use a simple test of superiority (without a predefined margin) to evaluate the primary outcome difference between the study groups. The decision to use a test of superiority was made with input from the data and safety monitoring board after they had seen unblinded data.

The primary analyses were performed using an intention-to-treat approach. A χ^2 test or Fisher exact test was used to compare the primary, secondary, and safety dichotomous outcomes. A nonparametric method (Mann-Whitney test) was used to compare the secondary continuous outcomes. The absolute differences in rates and 95% CIs between groups were calculated as Wald asymptotic or exact (Clopper-Pearson) confidence limits. For the secondary continuous outcomes, the differences in the median time and 95% confidence limits were computed based on 5000-bootstrap resampling. Univariable and multivariable logistic or Cox models were used to determine the effects of high-intensity NPPV for the primary, secondary, and safety outcomes compared with low-intensity NPPV.

The cumulative incidence for the time-to-event outcomes were estimated using the Kaplan-Meier method and compared using a log-rank test, including the incidence of need for endotracheal intubation, undergoing endotracheal intubation, the composite of endotracheal intubation or avoiding endotracheal intubation by crossover to high-intensity NPPV, and death within 28 days after randomization. The per-protocol analyses and sensitivity analyses with additional adjustment of forced expiratory volume in the first second of expiration (FEV_1) in the multivariable analyses were conducted to evaluate the robustness of the results from the primary analysis. The prespecified subgroup analysis (by age, sex, smoking history, and pH level at randomization) and post hoc comparisons (by $PaCO_2$ level at randomization, PaO_2:FIO_2 at randomization, respiratory rate at randomization, FEV_1 level, and Acute Physiology and Chronic Health Evaluation II score) were also performed. Repeated-measures analysis of variance with 2 factors (intervention group and time) was used to compare variables regarding ventilator settings and respiratory physiology between the high-intensity NPPV group and the low-intensity NPPV group at each time point.

Missing data were not imputed. Most of the reported *P* values are 2-sided; however, a 1-sided *P* value was used for the between-group rate difference for the need for endotracheal intubation. $P < .05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 4.2.3 (R Foundation for Statistical Computing).

Results

Patients

From January 3, 2019, to January 31, 2022, a total of 8148 patients with acute exacerbation of COPD were assessed for eligibility. Among these patients, 7848 were excluded and 300 were randomized and included in the primary analysis (Figure 1). Of the 300 patients, 147 were assigned to the high-intensity NPPV group and 153 to the low-intensity NPPV group. One patient in the low-intensity group received high-intensity NPPV because of a protocol violation and 1 patient in each group was lost to 90-day follow-up. The 90-day follow-up was completed on April 22, 2022.

Baseline characteristics were similar between groups (**Table 1** and eTables 2-4 in Supplement 3). The mean age was 73 years (SD, 10 years) and 68% of the patients were men. The mean FEV_1 was 36% predicted (SD, 12% predicted) (n = 243); 86% of patients were using long-acting inhaled bronchodilators and 79% were using inhaled corticosteroids. Most patients were able to complete bedside pulmonary function tests at baseline. However, in the high-intensity NPPV group, 27 patients (18%) were unable to complete the bedside pulmonary function test because of dyspnea and 4 (3%) declined to participate. In the low-intensity NPPV group, 24 patients (16%) were unable to complete the bedside pulmonary function test because of dyspnea and 2 (1%) declined to participate. There were no between-group differences for the number of patients who currently smoke and those who used long-term oxygen therapy.

Ventilator Interventions and Respiratory Physiology

The mean IPAP level at 2 hours was 25 cm H_2O (SD, 3 cm H_2O) (n = 146) in the high-intensity NPPV group vs 17 cm H_2O (SD, 2 cm H_2O) in the low-intensity NPPV group ($P < .001$). At 72 hours, the mean IPAP level was 25 cm H_2O (SD, 3 cm H_2O) (n = 137) in the high-intensity NPPV group and 18 cm H_2O (SD, 3 cm H_2O) (n = 141) in the low-intensity NPPV group ($P < .001$). The mean tidal volume at 2 hours was 11.0 mL/kg (SD, 3.4 mL/kg) of predicted body weight (n = 146) in the high-intensity NPPV group vs 7.7 mL/kg (SD, 2.2 mL/kg) of predicted body weight in the low-intensity NPPV group ($P < .001$) and at 72 hours was 11.5 mL/kg (SD, 3.3 mL/kg) of predicted body weight (n = 137) vs 8.2 mL/kg (SD, 2.0 mL/kg) of predicted body weight (n = 140), respectively ($P < .001$).

For the high-intensity NPPV group, the median daily use was 20 hours (IQR, 16-22 hours) on day 1, 18 hours (IQR, 14-22 hours; n = 141) on day 2, and 17 hours (IQR, 14-20 hours; n = 139) on day 3. For the low-intensity NPPV group, the median daily use was 18 hours (IQR, 14-21 hours) on day 1, 17 hours (IQR, 12-20 hours; n = 145) on day 2, and 16 hours (IQR, 12-20 hours; n = 143) on day 3. There was a statistically significant difference in daily NPPV use between the high-intensity NPPV group and the low-intensity NPPV group across the specified days ($P < .05$ for all tests; eTable 5 in Supplement 3). Further details regarding the ventilator interventions appear in eTables 5-6 in Supplement 3.

From 2 hours through 72 hours after randomization, the $PaCO_2$ level was lower in the high-intensity NPPV group (eTables 7-8 in Supplement 3). The mean $PaCO_2$ level at 72 hours was 53 mm Hg (SD, 12 mm Hg) in the high-intensity NPPV group (n = 135) compared with 64 mm Hg (SD, 11 mm Hg) in the low-intensity NPPV group (n = 139) ($P < .001$). At 72 hours, more patients in the high-intensity NPPV group (21.8% [32/147]) achieved normocapnia than those in the low-intensity NPPV group (4.6% [7/153]; $P < .001$; eTable 9 in Supplement 3).

Interim Analysis

A planned interim analysis was performed after the completion of primary outcome evaluations for 300 patients at discharge. The results showed that the primary outcome (the need for endotracheal intubation) differed significantly with a between-group difference of 9.0% (1-sided $P = .004$) within the context of a simple test of superiority without a predefined margin. The trial was terminated by the data and safety monitoring board and the trial steering committee based on the significant results from the interim analysis and the impracticality of continuing the trial during the COVID-19 pandemic, which posed substantial operational challenges and potential ethical concerns.

Primary Outcome

The primary outcome of meeting prespecified criteria for the need for endotracheal intubation occurred in 7 of 147 patients (4.8%) in the high-intensity NPPV group vs in 21 of 153 patients (13.7%) in the low-intensity NPPV group (absolute difference, −9.0% [95% CI, −15.4% to −2.5%], 1-sided $P = .004$; rate ratio, 0.35 [95% CI, 0.14 to 0.76]) (**Table 2**). After adjustment for respiratory tract infection, days from exacerbation to randomization, pH level at randomization, and PaO_2:FIO_2 at randomization, the need for endotracheal intubation remained significantly different between groups (adjusted rate ratio, 0.30 [95% CI, 0.11 to 0.69]). The analyses of the primary outcome in the per-protocol population and the sensitivity analyses were consistent with the primary analysis (eTables 10-11 in Supplement 3).

No treatment effect varied significantly between the study groups across the prespecified subgroups of age, sex, smoking history, and pH level at randomization or across the post hoc subgroups of $PaCO_2$ level at randomization, PaO_2:FIO_2 at randomization, respiratory rate at randomization, FEV_1 level, and Acute Physiology and Chronic Health Evaluation II score (**Figure 2**) (eFigure 1 and eTable 12 in Supplement 3). In addition, the endotracheal intubation rate did not significantly differ between groups (3.4% [5/147] in the high-intensity NPPV group vs 3.9% [6/153] in the low-intensity NPPV group; absolute difference, −0.5% [95% CI, −4.8% to 3.7%], $P = .81$; rate ratio, 0.87 [95% CI, 0.25 to 2.72]). The reasons for meeting the prespecified criteria for endotracheal intubation appear in eTable 13 and the reasons for undergoing endotracheal intubation appear in eTable 14 in Supplement 3.

Secondary Outcomes

The composite of endotracheal intubation or avoiding endotracheal intubation by crossover to high-intensity NPPV was significantly lower in the high-intensity NPPV group (3.4% [5/147]) than in the low-intensity NPPV group (11.1% [17/153]) (absolute difference, −7.7% [95% CI, −13.5% to −1.9%], $P = .01$; rate ratio, 0.31 [95% CI, 0.10 to 0.76]). Of the 21 patients in the low-intensity group who met the prespecified criteria for endotracheal intubation, 13 (61.9%) crossed over to high-intensity NPPV (Figure 1 and eFigure 2 in Supplement 3). Of these 13 patients, 2 (15.4%) were intubated and 11 (84.6%) were not intubated. With an increasing level of IPAP and tidal volume, the pH and $PaCO_2$ levels remained unchanged after 2 hours in intubated patients and were improved in nonintubated patients (eTable 15 in Supplement 3). The other 13 secondary outcomes did not differ significantly between groups (Table 2 and **Figure 3**) (eTables 10-11 and eFigure 3 in Supplement 3).

Table 1. Baseline Characteristics of the Participants

	Noninvasive positive pressure ventilation (NPPV)	
	High intensity (n = 147)	Low intensity (n = 153)
Age, mean (SD), y	73 (9)	73 (10)
Sex, No. (%)		
Male	100 (68)	103 (67)
Female	47 (32)	50 (33)
Height, mean (SD), cm	165 (8)	164 (8)
Body weight, mean (SD), kg		
Actual	65 (13)	64 (14)
Predicted[a]	60 (9)	59 (9)
Body mass index, mean (SD)[b]	24 (5)	24 (5)
COPD-related characteristics[c]		
Smoking history		
Ever smoked, No. (%)	90 (61)	98 (64)
Currently smoke, No. (%)	48 (33)	63 (41)
Median (IQR) [total], pack-years	40 (20-60) [n = 90]	30 (20-50) [n = 98]
Pulmonary function[d]		
FEV_1, mean (SD) [total], % predicted	35 (12) [n = 116]	38 (12) [n = 127]
Ratio of FEV_1 to FVC, mean (SD) [total]	47 (12) [n = 116]	48 (11) [n = 127]
Measured within previous 1 y, No. (%)	47 (32)	52 (34)
Measured at hospital discharge, No. (%)	69 (47)	75 (49)
Disease course, median (IQR), y	15 (10-20)	10 (9-30)
Treatment use, No. (%)		
Long-acting inhaled bronchodilators	124 (84)	133 (87)
Inhaled corticosteroids	116 (79)	122 (80)
Long-term oxygen therapy[e]	85 (58)	98 (64)
Long-term home NPPV[f]	28 (19)	32 (21)
Previous NPPV	81 (55)	89 (58)
Comorbidities, No. (%)[c]		
Chronic heart failure	73 (50)	70 (46)
Hypertensive heart disease	65 (44)	71 (46)
Ischemic heart disease	44 (30)	44 (29)
Diabetes	21 (14)	25 (16)
Obstructive sleep apnea	16 (11)	12 (8)
Atrial fibrillation	15 (10)	10 (7)
Cerebrovascular disease	10 (7)	14 (9)
Chronic kidney failure	6 (4)	3 (2)
Prior myocardial infarction	4 (3)	1 (1)
Peripheral vascular disease	2 (1)	3 (2)
Prior percutaneous coronary intervention	2 (1)	1 (1)
Exacerbation-related characteristics, No. (%)		
Respiratory infection	103 (70)	100 (65)
Pneumonia	31 (21)	38 (25)
Heart failure	50 (34)	46 (30)
Exposure to air pollutants	3 (2)	4 (3)
Undetermined	10 (7)	13 (9)
Time from exacerbation to randomization, median (IQR), d[g]	6 (3-10)	6 (3-10)
Arterial blood gas levels at randomization, mean (SD)[h]		
pH	7.31 (0.06)	7.31 (0.05)
$Paco_2$, mm Hg	79 (15)	79 (15)
Pao_2:Fio_2, mm Hg	206 (59)	200 (51)
Bicarbonate, mmol/L	38 (7)	39 (7)

(continued)

Table 1. Baseline Characteristics of the Participants (continued)

	Noninvasive positive pressure ventilation (NPPV)	
	High intensity (n = 147)	Low intensity (n = 153)
Disease status score, mean (SD)		
Modified Medical Research Council dyspnea scale[i,j]	3 (1)	3 (1)
COPD Assessment Test[j,k]	25 (6)	26 (7)
Acute Physiology and Chronic Health Evaluation II[l]	17 (4)	17 (4)

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second of expiration; FIO_2, fraction of inspired oxygen; FVC, forced vital capacity.

[a] Used to determine tidal volume. For male patients, this was calculated as 50 + 0.91 (centimeters of height −152.4); female patients, 45.5 + 0.91 (centimeters of height −152.4).

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Obtained from the patients, their next of kin, or the medical record.

[d] If it had been collected within the previous year, the pulmonary function measure was considered valid. If the patient did not have a pulmonary function result within the previous year, a bedside pulmonary function test was required when patients were going to be discharged. However, 27 patients (18%) were unable to finish the bedside test and 4 (3%) refused to participate in the high-intensity NPPV group and 24 (16%) and 2 (1%), respectively, in the low-intensity NPPV group.

[e] Patients receiving oxygen therapy for at least 3 months prior to the current hospitalization.

[f] Patients receiving home NPPV for at least 3 months prior to the current hospitalization.

[g] An exacerbation was defined as an acute worsening of respiratory symptoms that result in additional therapy and was confirmed by an attending physician.

[h] Recorded after receiving low-intensity NPPV for 6 hours.

[i] The dyspnea scale ranges from a score of 0 to 4; higher scores indicate more severe breathlessness. A score of 3 indicates that patients would feel breathless after walking for a while before the current exacerbation.

[j] One patient in the low-intensity NPPV group was unable to finish the assessments due to a poor level of consciousness; the scores for all questions were calculated at the worst level (ie, the Modified Medical Research Council dyspnea scale score was recorded as 4 and the COPD Assessment Test score was recorded as 40).

[k] The score range is from 0 to 40; higher scores indicate more severe disease. A score of 25 indicates that prior to the current exacerbation, patients had all of the following: cough, phlegm, chest tightness, breathless, limited activities, poor sleep quality, and low energy.

[l] The score range is from 0 to 71; higher scores indicate more severe disease and higher mortality risk. A score of 17 indicates that the illness level of the patient was quite severe; the predicted hospital mortality was around 20%.

Safety Outcomes

Abdominal distention occurred more frequently in the high-intensity NPPV group (37.4% [55/147]) than in the low-intensity NPPV group (25.5% [39/153]) (**Table 3**). There was intolerance to NPPV because of abdominal distention (3.4% [5/147] in the high-intensity NPPV group vs 0.7% [1/153] in the low-intensity NPPV group), but no patients requested removal of NPPV due to abdominal distension. There were no cases of pneumothorax in either group. Other prespecified adverse effects related to NPPV did not differ significantly between groups (eTable 16 in Supplement 3).

Serious adverse events were rare in both groups (Table 3). Of 147 patients in the high-intensity NPPV group, 6 (4.1%) experienced severe alkalosis (defined as a pH level >7.55) compared with 0 of 153 patients in the low-intensity NPPV group. Other prespecified serious adverse events did not differ significantly between groups (eTable 16 in Supplement 3).

Discussion

In this randomized clinical trial conducted in patients with an acute exacerbation of COPD and a $PaCO_2$ level greater than 45 mm Hg after initially receiving 6 hours of low-intensity NPPV when admitted to respiratory non-ICU wards, high-intensity NPPV significantly reduced the number of patients who met prespecified criteria for needing endotracheal intubation during hospitalization compared with low-intensity NPPV. However, the endotracheal intubation rate did not differ between groups. High-intensity NPPV resulted in more abdominal distention, but did not lead to severe intolerance of NPPV or removal from NPPV. Except for mildly higher rates of severe alkalosis caused by high-intensity NPPV, severe adverse events were rare and similar between groups.

Patients in the current trial had acute hypercapnic respiratory failure that was superimposed on preexisting chronic hypercapnic respiratory failure (as shown by their high $PaCO_2$ and elevated bicarbonate levels), leading to relatively mild respiratory acidosis. Moreover, more than 55% of the patients had prior use of NPPV, underscoring the severity of chronic hypercapnic respiratory failure. Differing from previous trials (eTable 17 in Supplement 3),[3,22] patients in the current trial had higher baseline $PaCO_2$ levels, but the pH levels exhibited only a slight decrease from baseline and were higher than those reported by Brochard et al.[22] This is mainly because bicarbonate levels were already elevated during the stable stage due to kidney compensation for chronic hypercapnic respiratory failure. By the time of randomization, bicarbonate levels had further increased along with elevated $PaCO_2$ levels because the median 6-day interval from exacerbation to randomization provided sufficient time for further kidney compensation.

The need for endotracheal intubation in the low-intensity NPPV group was 13.7%, which is consistent with the rates reported in previous studies. For instance, Plant et al[3] found an endotracheal intubation rate of 15% among 118 patients with an acute exacerbation of COPD who were receiving NPPV, whereas in a large retrospective cohort study, Lindenauer et al[2] reported an endotracheal intubation rate of 15.3% for 17 978 patients who were receiving NPPV.

The lower rate of endotracheal intubation (4.8%) with use of high-intensity NPPV in the current study may be due to several factors. First, high-intensity NPPV may provide more support for the inspiratory effort in patients and alleviate

Table 2. Primary and Secondary Outcomes

	Noninvasive positive pressure ventilation (NPPV)				Ratio measure (95% CI)[b]	
	High intensity (n = 147)	Low intensity (n = 153)	Unadjusted absolute difference (95% CI)[a]	*P* value	Unadjusted	Adjusted[c]
Primary outcome[d]						
Need for endotracheal intubation during hospitalization, No. (%)	7 (4.8)	21 (13.7)	−9.0 (−15.4 to −2.5)	.004[e]	0.35 (0.14 to 0.76)	0.30 (0.11 to 0.69)
Secondary outcomes[d]						
Endotracheal intubation during hospitalization, No. (%)	5 (3.4)	6 (3.9)	−0.5 (−4.8 to 3.7)	.81	0.87 (0.25 to 2.72)	0.88 (0.24 to 2.97)
Endotracheal intubation at 28 d, No. (%)						
Met prespecified criteria for the need for intubation	7 (4.8)	21 (13.7)	−9.0 (−15.4 to −2.5)	.008	0.35 (0.14 to 0.76)	0.30 (0.11 to 0.69)
Intubated	5 (3.4)	6 (3.9)	−0.5 (−4.8 to 3.7)	.81	0.87 (0.25 to 2.72)	0.88 (0.24 to 2.97)
Composite of endotracheal intubation or avoiding intubation, No. (%)[f]	5 (3.4)	17 (11.1)	−7.7 (−13.5 to −1.9)	.01	0.31 (0.10 to 0.76)	0.27 (0.08 to 0.69)
NPPV weaning success, No. (%)	97 (66.0)	104 (68.0)	−2.0 (−12.6 to 8.7)	.71	0.97 (0.80 to 1.12)	0.98 (0.81 to 1.13)
Mortality, No./total (%)						
During hospitalization	1/147 (1.0)	4/153 (2.6)	−1.9 (−6.0 to 1.4)[g]	.37[h]	0.26 (0.01 to 1.72)	0.25 (0.01 to 1.78)
At 28 d	2/147 (1.4)	3/153 (2.0)	−0.6 (−4.5 to 3.2)[g]	>.99[h]	0.69 (0.09 to 3.97)	0.81 (0.10 to 5.37)
At 90 d	6/146 (4.1)	6/152 (4.0)	0.2 (−4.3 to 4.6)	.94	1.04 (0.33 to 3.11)	1.00 (0.31 to 3.07)
ICU admission, No. (%)	4 (2.7)	5 (3.3)	−0.6 (−5.2 to 4.0)[g]	>.99[h]	0.83 (0.21 to 2.98)	0.81 (0.19 to 3.01)
Discharged alive from the hospital, No. (%)	143 (97.3)	144 (94.1)	3.2 (−1.4 to 7.7)	.18	1.03 (0.98 to 1.05)	1.03 (0.97 to 1.05)
Length of hospital stay, median (IQR), d						
Overall	10 (8 to 13)	10 (9 to 15)	0 (−1 to 1)[i]	.22	HR, 1.10 (0.88 to 1.38)	HR, 1.10 (0.88 to 1.38)
After randomization	9 (7 to 13)	10 (8 to 14)	−1 (−2 to 1)[i]	.09	HR, 1.08 (0.86 to 1.35)	HR, 1.08 (0.86 to 1.36)
Invasive ventilator-free days at 28 d, median (IQR), d	28 (28 to 28)	28 (28 to 28)	0	.79	NA[j]	NA[j]
ICU-free days at 28 d, median (IQR), d	28 (28 to 28)	28 (28 to 28)	0	.77	NA[j]	NA[j]
Hospital readmission at 90 d, No./total (%)	21/146 (14.4)	22/152 (14.5)	−0.1 (−8.1 to 7.9)	.98	0.99 (0.56 to 1.68)	0.93 (0.52 to 1.60)

Abbreviations: HR, hazard ratio; ICU, intensive care unit; NA, not applicable.

[a] Expressed as percentages unless otherwise indicated.

[b] Expressed as a rate ratio unless otherwise indicated.

[c] Adjusted for respiratory tract infection, days from exacerbation to randomization, pH level at randomization, and ratio of Pao_2 to fraction of inspired oxygen (Fio_2) at randomization.

[d] The outcome definitions appear in the eMethods in Supplement 3.

[e] This is a 1-sided *P* value. All other *P* values are 2-sided.

[f] In the high-intensity NPPV group, defined as the incidence of endotracheal intubation. In the low-intensity NPPV group, defined as the composite incidence of endotracheal intubation or avoiding intubation by crossover to high-intensity NPPV.

[g] Indicates a Clopper-Pearson 95% CI for the rate difference.

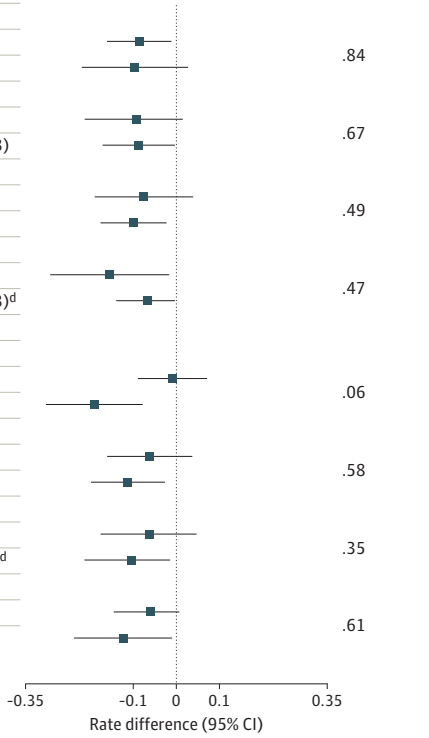
[h] The Fisher exact test was used to calculate the *P* value.

[i] The 95% CIs for the median time differences were estimated using resampling with 5000 bootstrap samples.

[j] The estimation was not applicable for the Cox regression model because the count of days was interrupted for invasive ventilator–free days and ICU-free days.

Figure 2. Prespecified and Post Hoc Subgroup Analyses for the Primary Outcome of Need for Endotracheal Intubation in the Noninvasive Positive Pressure Ventilation (NPPV) Groups

Subgroup[a]	No./total (%) of patients: High-intensity NPPV	No./total (%) of patients: Low-intensity NPPV	Rate difference (95% CI)[b]	*P* value for interaction[c]
Prespecified				
Sex				
Male	4/100 (4)	13/103 (13)	-0.09 (-0.16 to -0.01)	.84
Female	3/47 (6)	8/50 (16)	-0.10 (-0.22 to 0.03)	
Age group, y				
<70	2/57 (4)	7/55 (13)	-0.09 (-0.21 to 0.02)[d]	.67
≥70	5/90 (6)	14/98 (14)	-0.09 (-0.17 to -0.003)	
Ever smoked				
No	4/57 (7)	8/55 (15)	-0.08 (-0.19 to 0.04)	.49
Yes	3/90 (3)	13/98 (13)	-0.10 (-0.18 to -0.02)	
pH level at randomization[e]				
<7.3	6/63 (10)	13/52 (25)	-0.15 (-0.29 to -0.02)	.47
≥7.3	1/84 (1)	8/101 (8)	-0.07 (-0.14 to -0.003)[d]	
Post hoc				
Level of $Paco_2$ at randomization, mm Hg[e]				
<80	4/80 (5)	5/85 (6)	-0.01 (-0.09 to 0.07)[d]	.06
≥80	3/67 (4)	16/68 (24)	-0.19 (-0.30 to -0.08)	
Ratio of Pao_2 to Fio_2 at randomization, mm Hg[e]				
<200	5/66 (8)	11/80 (14)	-0.06 (-0.16 to 0.04)	.58
≥200	2/81 (2)	10/73 (14)	-0.11 (-0.20 to -0.03)	
FEV_1, % predicted				
<35	3/57 (5)	7/61 (11)	-0.06 (-0.18 to 0.05)[d]	.35
≥35	1/59 (2)	8/66 (12)	-0.10 (-0.21 to -0.01)[d]	
APACHE II score				
<17	1/76 (1)	6/81 (7)	-0.06 (-0.15 to 0.01)[d]	.61
≥17	6/71 (8)	15/72 (21)	-0.12 (-0.24 to -0.01)	



APACHE indicates Acute Physiology and Chronic Health Evaluation; FEV_1, forced expiratory volume in the first second of expiration; Fio_2, fraction of inspired oxygen.

[a]The prespecified subgroups were determined by age, sex, smoking history, and pH level at randomization. The post hoc subgroups were determined by $Paco_2$ level at randomization, Pao_2:Fio_2 at randomization, FEV_1 level, and APACHE II score.

[b]A rate difference of less than 0 indicates a reduced need for endotracheal intubation and a rate difference greater than 0 indicates an increased need for endotracheal intubation.

[c]The *P* values were calculated using the test for the subgroup × treatment interaction.

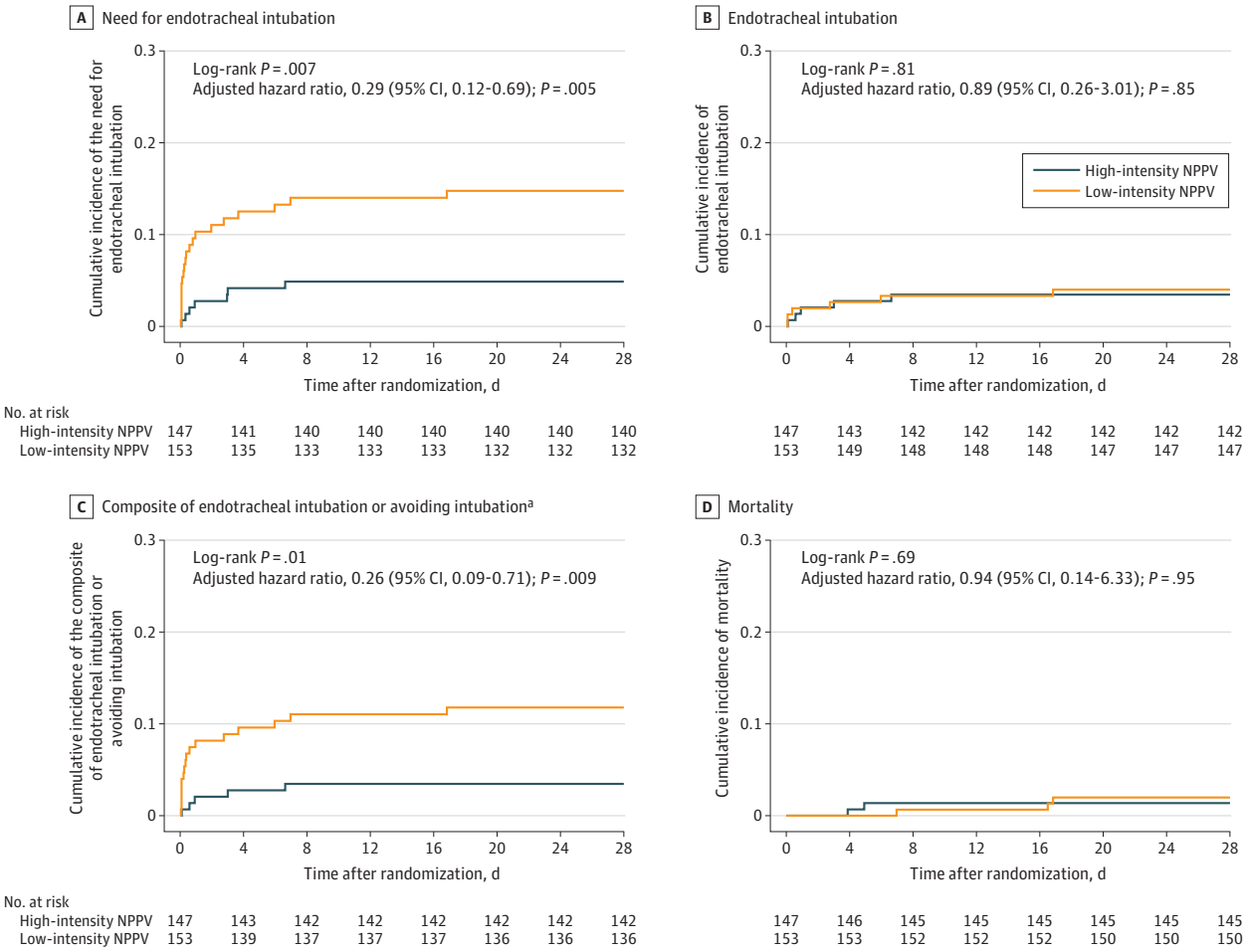
[d]Indicates a Clopper-Pearson 95% CI for the rate difference.

[e]Randomization occurred after all patients received 6 hours of low-intensity NPPV during the run-in period.

dyspnea.[14,16,19] Second, high-intensity NPPV provides greater pressure support and delivers a higher tidal volume, offsetting the dead space associated with the face mask and augmenting alveolar ventilation. The level of $Paco_2$ can be reduced toward normocapnia only if patients can tolerate high-intensity NPPV.[19] In the current trial, most patients tolerated high-intensity NPPV and only 7.5% had severe intolerance, resulting in a decrease in $Paco_2$ level to approximately 50 mm Hg at 72 hours. In contrast, low-intensity NPPV provides relatively less pressure support and delivers a smaller tidal volume, limiting the improvement in alveolar ventilation and resulting in a limited decrease in $Paco_2$ level. In the current trial, $Paco_2$ level remained at 64 mm Hg at 72 hours in the low-intensity NPPV group. Third, high-intensity NPPV required patients to receive continuous NPPV, and produced a longer median daily duration of NPPV over the first 3 days compared with low-intensity NPPV. This extended duration of NPPV use may have further deceased $Paco_2$ levels at 72 hours. Fourth, through reduced activation of the renin-angiotensin-aldosterone system, decreasing hypercapnia may result in less fluid retention and thus reduced airway edema, possibly further improving ventilatory status.[13,23] Fifth, decreased hypercapnia may aid in restoring the depressed response of central chemoreceptors to an increase in $Paco_2$ levels by reducing the concentration of cerebrospinal fluid bicarbonate, and decreased hypercapnia may aid in recovering diaphragm contractile function.[24,25] Both of these effects may also help to improve ventilatory status.

In the current study, the endotracheal intubation rate did not differ between groups, presumably due to the allowed crossover of patients from low-intensity NPPV to high-intensity NPPV if they met criteria for the need for endotracheal intubation. Among patients in the low-intensity group who met criteria for the need for endotracheal intubation and who crossed over to high-intensity NPPV, most had improvements in pH and $Paco_2$ levels with increases in IPAP level and

Figure 3. Kaplan-Meier Curves for 4 Outcomes in the Noninvasive Positive Pressure Ventilation (NPPV) Groups



All patients were observed to an event or at 28 days.

[a]Patients in the low-intensity NPPV group crossed over to high-intensity NPPV.

tidal volume, and 11 of 13 (85%) avoided endotracheal intubation. In this regard, the current trial could be interpreted as showing no difference between the patients starting with a strategy of low-intensity NPPV who were allowed crossover to high-intensity NPPV and the patients starting with high-intensity NPPV.

The patients in the high-intensity NPPV group had more abdominal distension due to the high IPAP, which can cause gas inflation into the stomach if it exceeds the lower esophageal sphincter pressure.[26,27] However, the presence of abdominal distension did not significantly affect the use of high-intensity NPPV. Intolerance to NPPV due to abdominal distension did not differ significantly between groups and no patients requested removal of NPPV because of abdominal distension in either group. High-intensity NPPV was associated with a mildly higher proportion of severe alkalosis, but no related severe adverse effects (such as myocardial ischemia, arrhythmias, delirium, and seizures[28]) were observed in the current trial. Moreover, only 6 patients experienced severe alkalosis (defined as having a pH level >7.55).

High-intensity NPPV may potentially increase the risk of ventilator-induced lung injury with a higher IPAP level. However, no patients had a pneumothorax in the current trial, which may be due to exclusion of patients with emphysematous bullae and setting an upper limit of IPAP level at 30 cm H_2O.[29] Consistent with the findings from the current study, no pneumothorax has been reported in previous studies including stable patients with COPD.[14,30] There may be potential risks of dynamic hyperinflation and gas trapping associated with higher tidal volumes. However, the high-intensity NPPV protocol used did not incorporate a high backup ventilatory rate and the actual respiratory rate exhibited only a minor increase, allowing patients to have sufficient expiratory time to achieve lung emptying.[31] This approach likely contributed to a reduced likelihood of worsening dynamic hyperinflation.[19] In addition, the applicability of the findings from the current study is best limited to patients experiencing only a slight increase in respiratory rate.

The strengths of this trial include its large size, multicenter design, sealed randomization, clear enrollment criteria,

Table 3. Safety Outcomes and Serious Adverse Events

	Noninvasive positive pressure ventilation (NPPV), No. (%)	
	High intensity (n = 147)	Low intensity (n = 153)
Safety outcomes[a]		
Complications related to NPPV		
Abdominal distension	55 (37.4)	39 (25.5)
Nasal or oral dryness	44 (29.9)	46 (30.1)
Severe air leakage[b]	26 (17.7)	17 (11.1)
Severe intolerance to NPPV[c]	11 (7.5)	6 (3.9)
Inability to remove respiratory secretions	8 (5.4)	9 (5.9)
Nasal or facial skin necrosis	3 (2.0)	6 (3.9)
Claustrophobia	3 (2.1)	4 (2.6)
Intolerance to NPPV because of abdominal distension	5 (3.4)	1 (0.7)
Aspiration	1 (0.7)	1 (0.7)
Hypotension	2 (1.4)	0
Conjunctivitis	0	1 (0.7)
Serious adverse events		
Severe alkalosis	6 (4.1)	0
Gastrointestinal tract bleeding	0	3 (2.0)
Nosocomial pneumonia	0	2 (1.3)
Septic shock	1 (0.7)	1 (0.7)
Multiple organ failure	1 (0.7)	1 (0.7)
Cardiac arrest	0	2 (1.3)

[a] The outcome definitions appear in the eMethods in Supplement 3.

[b] Defined as an unintentional air leakage volume exceeding 25 L/min.

[c] Defined as a tolerance level of 0 or 1; 0 indicates very poor tolerance requiring immediate discontinuation of NPPV and 1 indicates poor tolerance, but did not require immediate discontinuation of NPPV.

well-defined protocol, and strict criteria for defining the need for endotracheal intubation with external validation by 3 independent experts blinded to the intervention.

Limitations

This study has several limitations. First, the study was prematurely halted after enrolling half of the intended participants, following the recommendation of the data and safety monitoring board to terminate the trial. This decision to terminate the trial was informed by the results of the prespecified interim analysis, which revealed a substantial and statistically significant difference in the primary outcome between the study groups. In addition, unforeseen challenges (including slower recruitment rates and the extensive disruptions caused by the COVID-19 pandemic) contributed to the premature cessation of the study.

Second, because of the intervention performed in this trial, treatment allocation was not blinded for all investigators and the attending physicians, but was blinded to the independent statistician from the data and safety monitoring board, which may have led to possible bias.

Third, because randomization was not stratified by participating center, unbalanced baseline characteristics may have occurred at some centers. However, the overall baseline disease severity was well-balanced between groups. Fourth, the trial was not powered to detect differences in mortality because crossover from low-intensity NPPV to high-intensity NPPV was permitted for patients who met the prespecified criteria for endotracheal intubation, reducing the likelihood of between-group differences in endotracheal intubation.

Fifth, our findings may not be generalizable to patients with evident emphysematous bullae and presence of restrictive ventilatory dysfunction (eg, pulmonary consolidation) because these patients were excluded from this trial.

Conclusions

Patients with COPD and persistent hypercapnia in the high-intensity NPPV group (vs patients in the low-intensity NPPV group) were significantly less likely to meet criteria for the need for endotracheal intubation; however, patients in the low-intensity NPPV group were allowed to crossover to high-intensity NPPV, and the between-group rate of endotracheal intubation was not significantly different.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Luo, Yichong Li, Shi, Cao, C. Wang.
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REFERENCES

1. Chandra D, Stamm JA, Taylor B, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. *Am J Respir Crit Care Med*. 2012;185(2):152-159. doi:10.1164/rccm.201106-1094OC

2. Lindenauer PK, Stefan MS, Shieh MS, Pekow PS, Rothberg MB, Hill NS. Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease. *JAMA Intern Med*. 2014;174(12):1982-1993. doi:10.1001/jamainternmed.2014.5430

3. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*. 2000;355(9219):1931-1935. doi:10.1016/S0140-6736(00)02323-0

4. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2017;7(7):CD004104. doi:10.1002/14651858.CD004104.pub4

5. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J*. 2017;50(2):1602426. doi:10.1183/13993003.02426-2016

6. Schwarz SB, Magnet FS, Windisch W. Why high-intensity NPPV is favourable to low-intensity NPPV: clinical and physiological reasons. *COPD*. 2017;14(4):389-395. doi:10.1080/15412555.2017.1318843

7. Cao Z, Luo Z, Hou A, et al. Volume-targeted versus pressure-limited noninvasive ventilation in subjects with acute hypercapnic respiratory failure: a multicenter randomized controlled trial. *Respir Care*. 2016;61(11):1440-1450. doi:10.4187/respcare.04619

8. Jolliet P, Ouanes-Besbes L, Abroug F, et al; ECHO ICU Trial Investigators. A multicenter randomized trial assessing the efficacy of helium/oxygen in severe exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;195(7):871-880. doi:10.1164/rccm.201601-0083OC

9. Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease. Early use of non-invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: a multicentre randomized controlled trial. *Chin Med J (Engl)*. 2005;118(24):2034-2040.

10. Antón A, Güell R, Gómez J, et al. Predicting the result of noninvasive ventilation in severe acute exacerbations of patients with chronic airflow limitation. *Chest*. 2000;117(3):828-833. doi:10.1378/chest.117.3.828

11. Windisch W, Haenel M, Storre JH, Dreher M. High-intensity non-invasive positive pressure ventilation for stable hypercapnic COPD. *Int J Med Sci*. 2009;6(2):72-76. doi:10.7150/ijms.6.72

12. Windisch W, Storre JH, Köhnlein T. Nocturnal non-invasive positive pressure ventilation for COPD. *Expert Rev Respir Med*. 2015;9(3):295-308. doi:10.1586/17476348.2015.1035260

13. van der Leest S, Duiverman ML. High-intensity non-invasive ventilation in stable hypercapnic COPD: evidence of efficacy and practical advice. *Respirology*. 2019;24(4):318-328. doi:10.1111/resp.13450

14. Dreher M, Storre JH, Schmoor C, Windisch W. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. *Thorax*. 2010;65(4):303-308. doi:10.1136/thx.2009.124263

15. Dreher M, Ekkernkamp E, Walterspacher S, et al. Noninvasive ventilation in COPD: impact of inspiratory pressure levels on sleep quality. *Chest*. 2011;140(4):939-945. doi:10.1378/chest.11-0253

16. Lukácsovits J, Carlucci A, Hill N, et al. Physiological changes during low- and high-intensity noninvasive ventilation. *Eur Respir J*. 2012;39(4):869-875. doi:10.1183/09031936.00056111

17. Köhnlein T, Windisch W, Köhler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. *Lancet Respir Med*. 2014;2(9):698-705. doi:10.1016/S2213-2600(14)70153-5

18. Murphy PB, Rehal S, Arbane G, et al. Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial. *JAMA*. 2017;317(21):2177-2186. doi:10.1001/jama.2017.4451

19. Luo Z, Cao Z, Li Y, et al. Physiological effects of high-intensity versus low-intensity noninvasive positive pressure ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease: a randomised controlled trial. *Ann Intensive Care*. 2022;12(1):41. doi:10.1186/s13613-022-01018-4

20. Luo Z, Wu C, Li Q, et al; HAPPEN Collaboration Group. High-intensity versus low-intensity noninvasive positive pressure ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease (HAPPEN): study protocol for a multicenter randomized controlled trial. *Trials*. 2018;19(1):645. doi:10.1186/s13063-018-2991-y

21. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2019 report. Accessed April 5, 2023. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

22. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1995;333(13):817-822. doi:10.1056/NEJM199509283331301

23. de Leeuw PW, Dees A. Fluid homeostasis in chronic obstructive lung disease. *Eur Respir J Suppl*. 2003;46:33s-40s. doi:10.1183/09031936.03.00000603a

24. Altose MD, McCauley WC, Kelsen SG, Cherniack NS. Effects of hypercapnia and inspiratory flow-resistive loading on respiratory activity in chronic airways obstruction. *J Clin Invest*. 1977;59(3):500-507. doi:10.1172/JCI108665

25. Juan G, Calverley P, Talamo C, Schnader J, Roussos C. Effect of carbon dioxide on diaphragmatic function in human beings. *N Engl J Med*. 1984;310(14):874-879. doi:10.1056/NEJM198404053101402

26. Weiler N, Heinrichs W, Dick W. Assessment of pulmonary mechanics and gastric inflation pressure during mask ventilation. *Prehosp Disaster Med*. 1995;10(2):101-105. doi:10.1017/S1049023X00041807

27. Fitz-Clarke JR. Fast or slow rescue ventilations: a predictive model of gastric inflation. *Respir Care*. 2018;63(5):502-509. doi:10.4187/respcare.05620

28. Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders: second of two parts. *N Engl J Med*. 1998;338(2):107-111. doi:10.1056/NEJM199801083380207

29. Fan E, Del Sorbo L, Goligher EC, et al; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253-1263. doi:10.1164/rccm.201703-0548ST

30. Murphy PB, Brignall K, Moxham J, Polkey MI, Davidson AC, Hart N. High pressure versus high intensity noninvasive ventilation in stable hypercapnic chronic obstructive pulmonary disease: a randomized crossover trial. *Int J Chron Obstruct Pulmon Dis*. 2012;7:811-818. doi:10.2147/COPD.S36151

31. Blanch L, Bernabé F, Lucangelo U. Measurement of air trapping, intrinsic positive end-expiratory pressure, and dynamic hyperinflation in mechanically ventilated patients. *Respir Care*. 2005;50(1):110-123.