

A Multicenter Randomized Trial Assessing the Efficacy of Helium/Oxygen in Severe Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: During noninvasive ventilation (NIV) for chronic obstructive pulmonary disease (COPD) exacerbations, helium/oxygen (heliox) reduces the work of breathing and hypercapnia more than air/O₂, but its impact on clinical outcomes remains unknown.

Objectives: To determine whether continuous administration of heliox for 72 hours, during and in-between NIV sessions, was superior to air/O₂ in reducing NIV failure (25–15%) in severe hypercapnic COPD exacerbations.

Methods: This was a prospective, randomized, open-label trial in 16 intensive care units (ICUs) and 6 countries. Inclusion criteria were COPD exacerbations with PaCO₂ ≥ 45 mm Hg, pH ≤ 7.35, and at least one of the following: respiratory rate ≥ 25/min, PaO₂ ≤ 50 mm Hg, and oxygen saturation (arterial [SaO₂] or measured by pulse oximetry [SpO₂]) ≤ 90%. A 6-month follow-up was performed.

Measurements and Main Results: The primary endpoint was NIV failure (intubation or death without intubation in the ICU). The secondary endpoints were physiological parameters, duration of

ventilation, duration of ICU and hospital stay, 6-month recurrence, and rehospitalization rates. The trial was stopped prematurely (445 randomized patients) because of a low global failure rate (NIV failure: air/O₂ 14.5% [n = 32]; heliox 14.7% [n = 33]; *P* = 0.97, and time to NIV failure: heliox group 93 hours [n = 33], air/O₂ group 52 hours [n = 32]; *P* = 0.12). Respiratory rate, pH, PaCO₂, and encephalopathy score improved significantly faster with heliox. ICU stay was comparable between the groups. In patients intubated after NIV failed, patients on heliox had a shorter ventilation duration (7.4 ± 7.6 d vs. 13.6 ± 12.6 d; *P* = 0.02) and a shorter ICU stay (15.8 ± 10.9 d vs. 26.7 ± 21.0 d; *P* = 0.01). No difference was observed in ICU and 6-month mortality.

Conclusions: Heliox improves respiratory acidosis, encephalopathy, and the respiratory rate more quickly than air/O₂ but does not prevent NIV failure. Overall, the rate of NIV failure was low.

Clinical trial registered with www.clinicaltrials.gov (NCT 01155310).

Keywords: chronic obstructive pulmonary disease; noninvasive ventilation; helium; outcome

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At a Glance Commentary

Scientific Knowledge on the

Subject: During acute hypercapnic chronic obstructive pulmonary disease (COPD) exacerbation, inhaling a helium/oxygen (heliox) mixture has been shown to reduce airway resistance, PaCO_2 , intrinsic positive end-expiratory pressure, and work of breathing more than air/ O_2 during both spontaneous breathing and noninvasive ventilation (NIV). However, the impact of heliox on patient outcomes remains unclear.

What This Study Adds to the

Field: In the largest study to date on acute COPD exacerbation requiring NIV in the intensive care unit, using a protocolized duration of treatment with the gas mixtures, validated heliox compatible equipment, and strict predefined criteria for intubation, the overall failure rate with NIV is less than 15%. The study shows that heliox does not decrease the NIV failure rate, nor the length of stay in the intensive care unit and hospital compared with air/ O_2 . It has significant physiological effects that allow for a faster improvement.

Due to its ability to reduce the need for endotracheal intubation and mortality, noninvasive ventilation (NIV) has become a standard of care for acute exacerbation of chronic obstructive pulmonary disease (COPD) (1). However, NIV fails to avoid endotracheal intubation in approximately 25% of patients (2, 3), who thereafter experience a longer intensive care unit (ICU) and hospital stay, and have a higher mortality rate (1). Therefore, any adjunctive therapy likely to decrease the incidence of NIV failure would be a valuable asset. One such approach might be the inhalation of a helium/oxygen (heliox) mixture. Due to its low density, heliox reduces the resistance to flow in the airways, which in turn decreases the work of breathing (WOB) (4–7). In COPD, spontaneous breathing of heliox decreases airway resistance to flow (8) and WOB (9); a retrospective study documented a reduction of the intubation rate, hospital mortality, and length of stay (LOS) in the ICU in patients with acute exacerbation of

COPD (10). Furthermore, during NIV, heliox decreases PaCO_2 and dyspnea more than air/ O_2 (11), due to a reduction in airway resistance, intrinsic positive end-expiratory pressure, and WOB (9). However, two prospective randomized studies of NIV with heliox failed to show a reduction in the intubation rate and LOS in the ICU (12, 13). However, both studies were underpowered, and heliox was applied only during NIV sessions, the duration of which might have been insufficient.

The purpose of this study was to explore whether continuous inhalation of heliox over 72 hours, using specific equipment, could reduce NIV failure, mortality, and duration of ICU and hospital stays compared with standard air/ O_2 administration.

Some of the results of these studies have been previously reported in the form of an abstract (14).

Methods

This was an international, multicenter, prospective, randomized (computer-generated list), open-label, controlled, parallel group phase III study (ClinicalTrials.gov NCT 01155310).

The study was conducted in compliance with Good Clinical Practice guidelines, the Declaration of Helsinki, and the European Directive 2001/20/EC, after approval by the local ethics committees. Informed consent was provided by the patient whenever possible, or initially by next of kin with subsequent consent by the patient.

Patients

Patients with a diagnosis of COPD known or clinically suspected at ICU admission and requiring NIV for acute hypercapnic respiratory failure were recruited into the study using a pragmatic approach for the diagnosis because inclusion needed to be made in the intensive care setting in patients with acute respiratory failure who required urgent therapy. The diagnosis was mainly based on clinical history, arterial blood gases, and clinical presentation at time of admission. The eligibility criteria for NIV were uncompensated respiratory acidosis ($\text{PaCO}_2 \geq 45$ mm Hg and arterial pH ≤ 7.35) on arterial blood gases drawn on room air or supplemental O_2 , and at least one of the following: respiratory rate ≥ 25 breaths/min, $\text{PaO}_2 \leq 50$ mm Hg, and oxygen saturation (arterial $[\text{SaO}_2]$ or measured by pulse oximetry $[\text{SpO}_2]) \leq 90\%$.

Patients with severe pulmonary embolism, extensive pneumonia, or pneumothorax were not included. Complete eligibility criteria are listed in the online supplement (see Table E1 in the online supplement). Of note, do-not-intubate patients were not excluded, to better reflect real-life conditions because such patients might benefit from heliox administration, which aims to avoid intubation, and because death was part of the main endpoint and would capture the NIV failure. Eligible patients were randomly assigned by center to one of two study groups, receiving either heliox or air/ O_2 .

Endpoints

The primary objective was to evaluate the efficacy of heliox (using a 78%/22% mixture blended with 100% O_2 to adjust for oxygenation requirements) compared with conventional air/ O_2 in reducing NIV failure, which was defined as endotracheal intubation or death without intubation, in patients with COPD with severe hypercapnic exacerbation who were admitted to the ICU. The secondary objectives were to assess the physiological effects and safety of heliox (78%/22%) administration in the ICU, and the effects on outcome at ICU and hospitalization discharge and at 6 months. Analyses were repeated separately in the subgroup of NIV failures and the subgroup of NIV successes for the evaluation of the index ICU and hospital LOS.

Delivery of Treatment

During NIV, the gas mixtures were administered through an oro-nasal mask (Flexi Fit HC431; Fisher and Paykel Healthcare Ltd., Auckland, New Zealand) with a Hamilton-G5 ventilator with Heliox option (Hamilton Medical AG, Bonaduz, Switzerland) (15), with either heliox or air/ O_2 ; the first session started, at the latest, 90 minutes after randomization. The initial level of pressure support was set at 12 to 15 cm H_2O , with subsequent changes as needed. Flow trigger was set at its maximum sensitivity to patient effort. A positive end-expiratory pressure of 3 to 5 cm H_2O was used initially. Heliox 78%/22% was manufactured by Air Liquide Santé (Jouy-en-Josas, France) for the trial and was supplied in 50-liter cylinders (B50) pressurized at 200 bars. A minimum of 6 hours of NIV was required during the first 24 hours of study treatment. A minimum time of 30 minutes per NIV session was required during the study treatment. Between

NIV sessions, heliox was administered with a high-concentration O₂ facemask (Pulmanex Hi-OX₈₀; Cardinal Health, Dublin, OH), using a specifically designed blender (Sentry He/O₂; Cardinal Health) (16). Patients in the air/O₂ group received O₂ via the interface routinely used in the center. The heliox flow rate had to be adapted to the FiO₂ (12 L/min for FiO₂: 0.22–0.35, and 15 L/min for FiO₂: 0.36–0.50). In the air/O₂ group, O₂ titration was achieved by changes in the delivered O₂ flow rate. For both study groups, O₂ supplementation was titrated to maintain SpO₂ ≥ 90%. Heliox or air/O₂ was administered for a maximum of 72 hours (study design; see Figure E1 in the online supplement). Thereafter, patients in both groups received air/O₂ according to clinical needs. Physiological variables and encephalopathy score (17) were followed closely for 72 hours. If intubation was required in the heliox group patients, even within the 72 hours post-randomization, ventilation was performed with an air/O₂

mixture. Therefore, heliox was not administered to intubated patients.

There were no recommendations concerning supplemental O₂, antibiotic agents, prevention of deep vein thrombosis, steroids, and bronchodilators, but all concomitant medications were recorded to ensure similar management in the two arms.

The following steps were taken to compensate for the nonblinded nature of the study: (1) the decision to intubate was based on the presence of at least one major or two minor published criteria (18), detailed in the online supplement (see Table E1); and (2) an endpoint adjudication and safety committee reviewed cases of NIV failure for every 100 patients enrolled, in a blind manner, based on hospital reports and nurse charts, and determined whether the patient's signs and symptoms before intubation met intubation criteria. The committee could also inform the investigators of any methodology or safety issue, and was allowed to propose holding or interrupting the study.

Statistical Analysis of Clinical Data Collected

Study sample size estimation was based on a reduction in the NIV failure rate by heliox from 25 to 15%, resulting in a total of 670 patients with 90% power.

All analyses performed were described in the study protocol, and the statistical significance of the two-sided tests performed was 0.05. No formal interim analyses were planned other than monitoring by the adjudication and safety committee (as previously described).

The primary analysis of the primary efficacy criterion was conducted on the intention-to-treat (ITT) data set. The occurrences of NIV failure during the index ICU stay, as recorded by the investigators, were compared between study groups using the Pearson's χ^2 test, and its calculation was provided by SAS version 9.3 (SAS Institute, Cary, NC).

A two-step exploratory multivariate logistic regression was performed to identify the independent predictors of the

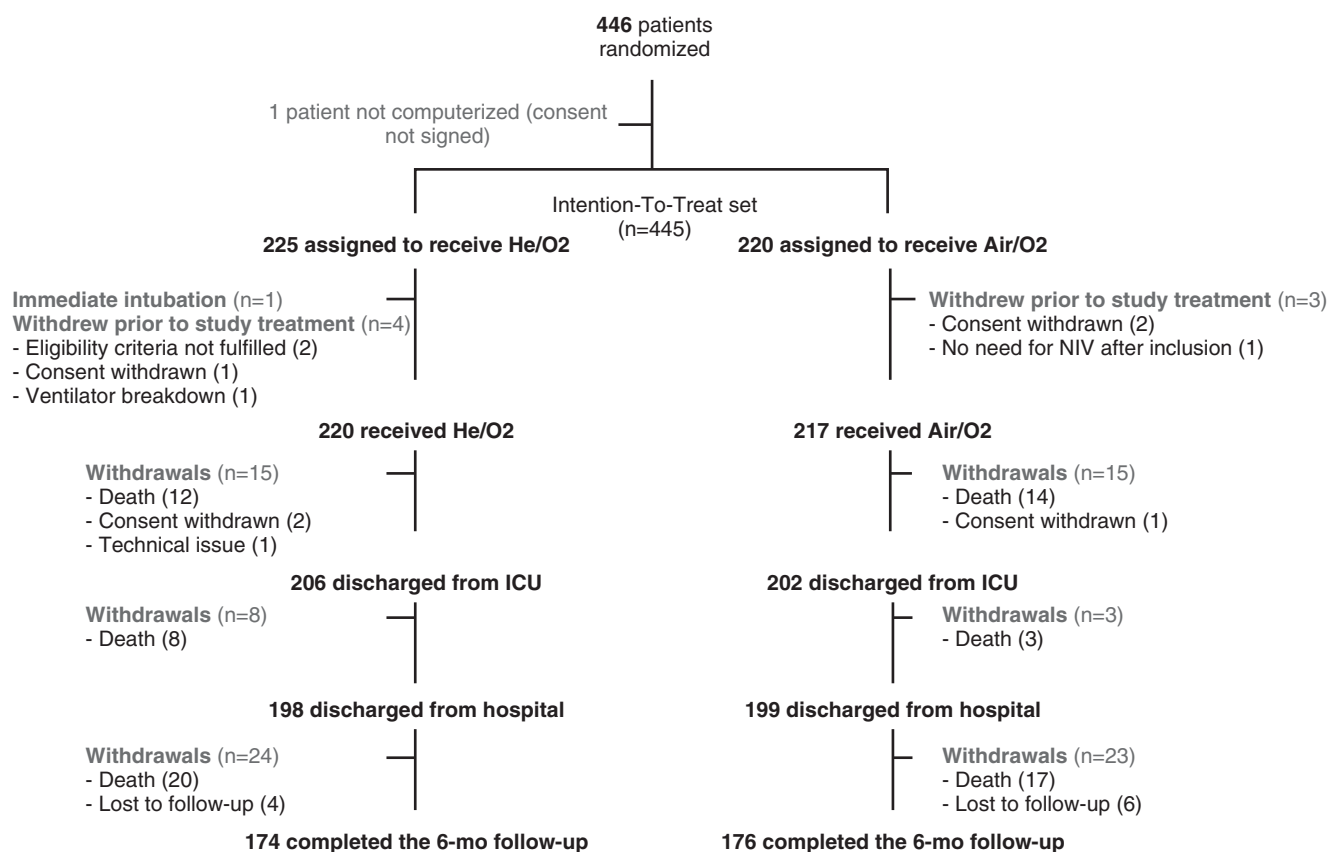


Figure 1. Consort diagram of the study. One patient allocated to receive helium/oxygen (heliox; He/O₂) was intubated a few minutes after randomization and did not receive heliox but completed the study. ICU = intensive care unit; NIV = noninvasive ventilation.

occurrences of NIV failure during the index ICU stay. Clinically relevant baseline predefined known risk factors were selected in a first step by separate two-factor (study group and investigated predictor) logistic regressions. All statistically significant factors or their interaction were then gathered in a multiple-factor model, including the study group, and the best final model was determined by backward elimination.

Student's *t* test was used to compare the cumulative duration of invasive ventilation in the subgroup of intubated patients and the ICU lengths of stay in the subgroups in whom NIV failed and NIV succeeded separately. In these latter subgroups, time to ICU discharge (or time to death during index ICU stay) after randomization was also described using survival methods and Kaplan-Meier's estimates; time to ICU discharge was

compared between study groups with the log-rank test.

The evolution of respiratory rate and arterial blood gases over time in both study groups during the index ICU stay was evaluated by a mixed analysis of covariance model on repeated measurements.

Results

The first patient was included in May 2010. Recruitment was stopped prematurely in April 2013 due to a low event rate, as reported by the endpoint validation and safety committee. A futility rule was then applied (the likelihood of finding a significant difference based on the total observed event rate had to be less than 30%) when a total of 445 patients were randomized over the 670 planned.

The study consort diagram is shown in Figure 1. Two hundred thirty-five patients were randomized in France (9 centers), 186 in Tunisia (2 centers), 11 in Italy (1 center), 8 in Switzerland (1 center), 4 in Belgium (2 centers), and 1 in the United Kingdom.

Table 1 outlines the baseline characteristics for both groups. COPD severity was assessable in 205 patients, with approximately 80% of these having the Global Initiative for Chronic Obstructive Lung Disease score of 3 or 4 (see Table E2). Of note, 35 patients had a pH > 7.35, whereas the inclusion criteria stipulated a pH ≤ 7.35. This was due to two reasons: (1) pH ≤ 7.35 was added as an inclusion criterion in an amendment to the initial protocol after reports from investigators that non-acidotic patients had been included; and (2) patients were selected on the entry criteria, and a few patients improved between

Table 1. Baseline Characteristics for the Intention-to-Treat Data Set

	Heliox (n = 225)	Air/O ₂ (n = 220)	All (n = 445)
Demographics and study disease characteristics			
Age, yr	68.9 ± 11.4	66.9 ± 11.4	67.9 ± 11.4
Sex (M/F), n	149/76	158/62	307/138
BMI, kg/m ²	25.7 ± 5.5	25.9 ± 6.3	25.8 ± 5.9
≤20, n (%)	36 (16)	34 (16)	70 (16)
>30, n (%)	52 (23)	51 (24)	103 (24)
Smoking status			
Current smokers, n (%)	85 (38)	94 (43)	179 (41)
Ex-smokers, n (%)	109 (49)	107 (49)	216 (49)
Pack-years	56 ± 28	61 ± 30	58 ± 29
Lung function			
Available PFTs, n (%)	124 (55)	107 (49)	231 (52)
FEV ₁ % predicted	36 ± 14	35 ± 15	36 ± 15
Stable PaCO ₂ , mm Hg	48 ± 9	49 ± 10	49 ± 10
Prior ICU admission			
Admission in ICU in the last 12 mo, n (%)	35 (16)	27 (12)	62 (14)
Intubated in the last 12 mo, n (%)	8 (4)	6 (3)	14 (3)
Characterization of the COPD exacerbation episode			
Main provenance			
Emergency room, n (%)	174 (77)	168 (76)	342 (77)
Medical ward, n (%)	23 (10)	30 (14)	53 (12)
Home, n (%)	22 (10)	16 (7)	38 (8)
Other, n (%)	6 (3)	6 (3)	12 (3)
Simplified Acute Physiology Score III	49.7 ± 7.9	48.8 ± 7.6	49.3 ± 7.8
Corresponding predicted mortality %	19.1 ± 12.1	17.8 ± 11.3	18.5 ± 11.7
Main causes of COPD exacerbation			
Infection, n (%)	113 (50)	115 (52)	228 (51)
Undetermined, n (%)	55 (24)	53 (24)	108 (24)
Cardiac, n (%)	35 (16)	30 (14)	65 (15)
Respiratory rate, breaths/min	29.3 ± 6.8	28.8 ± 5.4	29.0 ± 6.1
PaO ₂ , mm Hg	76.9 ± 36.7	73.2 ± 34.7	75.1 ± 35.8
PaCO ₂ , mm Hg	70.8 ± 15.7	68.1 ± 16.7	69.5 ± 16.2
pH	7.29 ± 0.05	7.30 ± 0.06	7.30 ± 0.06
Patients having received NIV before inclusion, n (%)	113 (50)	111 (50)	224 (50)
Do not intubate, n (%)	3 (1.3)	5 (2.3)	8 (1.8)

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; heliox = helium/oxygen; ICU = intensive care unit; NIV = noninvasive ventilation; PFTs = pulmonary function tests. Values are mean ± SD or number (%) of patients.

the time of enrollment and the first arterial blood gas after randomization. Eighty-four percent of the patients presented with at least one concomitant disease, the most frequent being arterial hypertension (49.9%) and diabetes (40.9%).

A total of 414 patients completed the study without major protocol deviations, and they were included in the per protocol (PP) analysis (see Table E3). The main reason for the major protocol deviations was that the study treatment administration was not performed according to the protocol for more than 50% of the treatment period, with this deviation occurring more frequently in the heliox group compared with the air/O₂ group (7.6% vs. 0.5%). NIV was started more than 120 minutes after randomization in five (2.2%) patients in the heliox group and six (2.7%) patients in the air/O₂ group. Detailed definition and full description of the PP population are provided in the online supplement (see Table E4). Treatment administered for the acute episode is summarized in Table E5. All the results are given in ITT analysis.

Main Endpoint: NIV Failure

Table 2 summarizes the main outcomes. The NIV failure rate was comparable between both groups (air/O₂: 14.5% [n = 32]; 95% confidence interval 10.2–19.9 vs. heliox: 14.7% [n = 33]; 95% confidence interval 10.3–20.0; *P* = 0.97; ITT, primary endpoint). Similar results were seen for the NIV failure rate in the PP data set (air/O₂: 14.9% vs. heliox: 15.1%; *P* = 0.96).

The mean ± SD time to NIV failure was 92.8 ± 128.4 hours in the heliox group (n = 33) and 51.5 ± 74.7 hours in the air/O₂ group (n = 32) (*P* = 0.12; *t* test). Figure 2A shows the Kaplan-Meier analysis of the time to NIV failure, that is, considering time of death or intubation for patients in whom NIV failed and time to ICU discharge for patients in whom NIV succeeded. Figure 2B shows the timeframe of intubation in patients in whom NIV failed during their index ICU stay; most of the patients were intubated within the first 2 days, but the time to NIV failure seemed to be delayed in patients who received heliox.

Criteria for intubation were comparable in the two groups. The evaluation of possible predictors of NIV failure during the index ICU stay showed that baseline pH was the only significant factor (*P* < 0.0001) (see Table E6). The intubation rate was 34% when baseline pH was ≤ 7.25, 10% if pH

Table 2. Main Outcomes for the Intention-to-Treat Data Set and the Intention-to-Treat Subgroups of Noninvasive Ventilation Failure or Success

ITT Data Set	Heliox (n = 225)	Air/O ₂ (n = 220)	P Value
NIV failure, n (%)	33 (14.7)	32 (14.5)	0.97*
Intubation, n (%)	31 (13.8)	32 (14.5)	0.82*
NIV duration, d	5.3 ± 4.2	5.1 ± 4.6	0.69 [†]
First 24 h, h	14.3 ± 6.1	13.9 ± 5.4	0.53 [†]
From 24th to 48th h, h	10.6 ± 4.6	10.4 ± 4.9	0.77 [†]
From 48th to 72nd h, h	9.8 ± 4.3	9.2 ± 4.1	0.27 [†]
Length of stay, d			
ICU stay	8.7 ± 6.7	10.2 ± 11.6	0.29 [‡]
Hospital stay	16.2 ± 11.6	17.0 ± 15.6	0.74 [‡]
Mortality, n (%)			
Index ICU	12 (5.3)	15 (6.8)	0.51*
Index hospitalization	20 (8.9)	18 (8.2)	0.79*
At 6 mo	40 (17.8)	35 (15.9)	0.60*
Subgroup of NIV failure (n = 33)			
Duration of ventilation, d			
IV	7.4 ± 7.6	13.6 ± 12.6	0.02 [†]
Total NIV prior to IV + IV	10.8 ± 8.9	16.0 ± 12.3	0.06 [†]
Length of stay, d			
ICU stay	15.8 ± 10.9	26.7 ± 21.0	0.01 [‡]
Hospital stay	22.6 ± 14.6	30.3 ± 19.7	0.10 [‡]
Mortality, n (%)			
Index ICU	12 (36.4)	14 (43.7)	0.54*
Index hospitalization	12 (36.4)	14 (43.7)	0.54*
At 6 mo	14 (42.5)	15 (46.8)	0.72*
Subgroup of NIV success (n = 192)			
NIV duration, d	5.5 ± 4.1	5.6 ± 4.6	0.87 [†]
Length of stay, d			
ICU stay	7.4 ± 4.6	7.3 ± 5.2	0.78 [‡]
Hospital stay	15.0 ± 10.6	14.7 ± 13.6	0.49 [‡]
Mortality, n (%)			
Index ICU	0	1 (0.5)	0.49 [§]
Index hospitalization	8 (4.2)	4 (2.1)	0.38 [§]
At 6 mo	26 (13.5)	20 (10.6)	0.39*

Definition of abbreviations: Heliox = helium/oxygen; ICU = intensive care unit; ITT = intention-to-treat; IV = invasive ventilation; NIV = noninvasive ventilation.

Values are mean ± SD or number (%) of patients.

*Pearson's χ^2 .

[†]Student's *t* test.

[‡]Log-rank.

[§]Fisher's exact test.

was > 7.25 but ≤ 7.35, and 3% if pH was > 7.35, and this rate was not influenced by the gas mixture received.

Physiological Effects

The time course of the main physiological variables is shown in Figures 3 and 4. In the heliox group, the respiratory rate decreased significantly faster during the first 12 hours, whereas pH increased and PaCO₂ decreased significantly more post-treatment until 72 hours. Pulse oximetry revealed no difference in oxygenation between groups. Figure 4 shows that the proportion of patients who had their encephalopathy score normalized was significantly higher during the first 48 hours in patients who received heliox.

Patients in Whom NIV Failed

Although ICU LOS was similar in both study groups (Figure 5 and Table 2), probability of prolonged ICU stay was higher in air/O₂ patients in whom NIV failed (air/O₂: 26.7 ± 21.0 d [n = 32] vs. heliox 15.8 ± 10.9 d [n = 33]; *P* = 0.01; log rank) (see Figure E3 and Table 2). When NIV failure resulted in intubation (n = 63), duration of invasive ventilation was also significantly higher in the air/O₂ group (air/O₂: 13.6 ± 12.6 d [n = 32] vs. heliox: 7.4 ± 7.6 d [n = 31]; *P* = 0.02; Student's *t* test) (Table 2). Reintubation occurred in 8 of the 32 air/O₂ group patients (25.0%) and 4 of the 31 heliox group patients (12.9%). All 8 re-intubated air/O₂ group patients died in ICU or

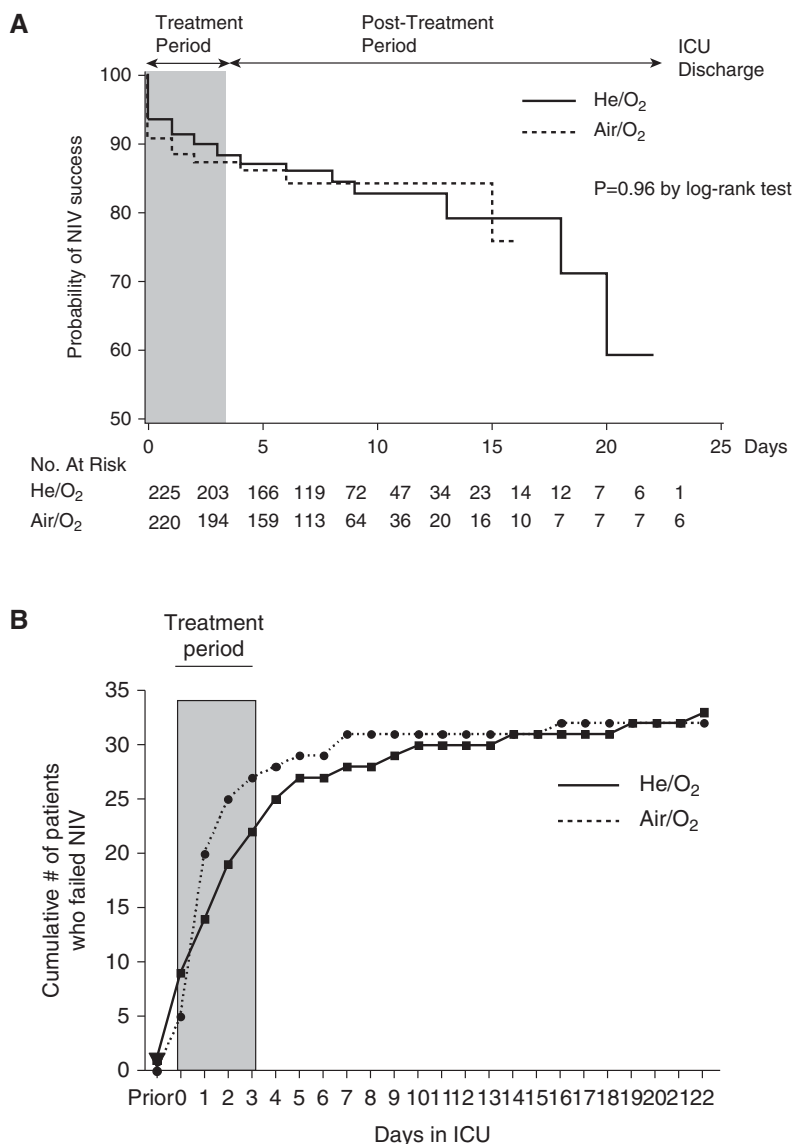


Figure 2. (A) Survival analysis of the time to noninvasive ventilation (NIV) failure (intention-to-treat data set). The analysis considers time to NIV failure as the time of occurrence of the NIV failure, whether patients in whom NIV succeeded are censored at the time of index intensive care unit (ICU) discharge or at the time of last contact if the patient was withdrawn before index ICU discharge. (B) Time frame of NIV failure by study group. Time to NIV failure was 93 ± 128 hours in the helium/oxygen (He/O₂) group ($n = 33$) and 52 ± 75 hours in the air/O₂ group ($n = 32$), $P = 0.12$ (t test).

during the 6-month follow-up, whereas it was the case for 2 of the 4 re-intubated heliox group patients. Lastly, in patients in whom NIV failed, no difference was observed in terms of total hospital LOS or ICU and 6-month mortality.

Safety

Table 3 summarizes the adverse events that occurred during the course of

the 6-month study. More details are provided in Table E7. No difference was documented between the two groups.

Administration of both gas mixtures was well tolerated: 7.1% of heliox NIV sessions and 11.5% of air/O₂ NIV sessions had to be discontinued, mainly because of mask intolerance, intubation, adverse events, and patient willingness. Heliox and air/O₂ ventilator-free administration had to be

discontinued in 7.2% and 3.5% of sessions, respectively (Table 3). The mean heliox consumption per patient was 37.2 ± 18.6 kJ, corresponding to approximately 4 ± 2 B50 per patient for the 72-hour treatment.

Six-Month Follow-up

No difference was noted between gas mixtures for the ICU, hospital, and 6-month mortality rates (Table 2).

Hospital readmissions (any ward) for COPD exacerbations during the 6-month follow-up occurred in 81 patients (18.2%) and were comparable for the two groups. During the 6-month follow-up, 28 patients (12%) of the heliox group, and 22 patients (10%) of the Air/O₂ group were re-admitted to the ICU for a COPD exacerbation, with a mean survival time of 204 ± 4 days and 177 ± 2 days after index ; hospitalization discharge, respectively. Seven patients (3.1%) of the heliox group and 6 patients (2.7%) of the air/O₂ group required invasive ventilation.

Discussion

The present study, which included 445 patients, was the largest to date on acute COPD exacerbation that requires NIV in the ICU with a 6-month follow-up. It was also the largest study on the medical use of heliox and the first to assess its continuous administration for up to 72 hours. Its main strengths were the number of patients, the continuous heliox administration, the protocolized duration of treatment with the gas mixtures, the use of validated heliox compatible equipment, the strict predefined criteria for intubation, and the 6-month follow-up. Although it confirmed the favorable physiological effects of heliox and the safety of its administration in the ICU, the study did not, however, demonstrate a reduction in the NIV failure rate nor in the LOS in the ICU and hospital compared with air/O₂. Although dealing with small numbers and subgroup analyses, both of which require great caution in their interpretation, the duration of mechanical ventilation and the ICU LOS were significantly shorter in the subgroup of patients who received heliox and in whom NIV failed.

The main finding of our study was that inhalation of heliox for up to 72 hours, during both NIV and spontaneous breathing, did not reduce the intubation rate in a population of patients with acute

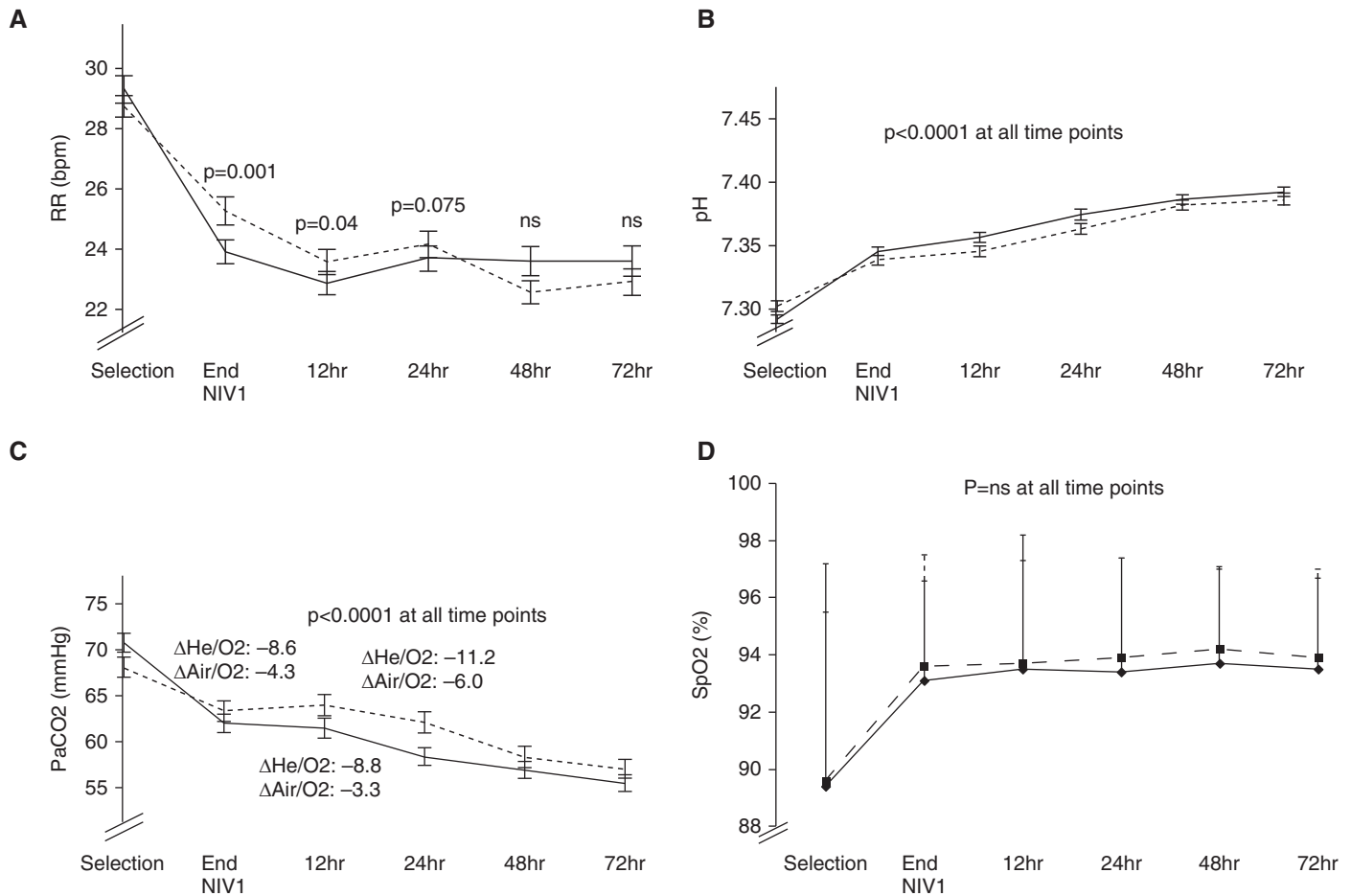


Figure 3. Physiological outcomes (intention-to-treat data set). (A) Respiratory rate (RR): a statistical difference is seen post-treatment onset until 12 hours (*t* test). (B) pH. (C) PaCO₂: overall treatment effect: $P < 0.0001$ at all time points (analysis of covariance). Absolute differences are shown in mm Hg for PaCO₂. (D) SpO₂ (room air or supplemental oxygen [O₂]): no difference is seen for SpO₂ at all time points. Helium/oxygen (He/O₂), solid lines; air/O₂, dashed lines. Values are mean $\pm$ 95% confidence intervals for RR, pH, and PaCO₂, and mean $\pm$ SD for SpO₂. NIV = noninvasive ventilation; ns = not significant.

exacerbation of COPD. NIV failure rates were similar for both gas mixtures, even in patients with severe respiratory acidosis (pH < 7.30). Two previous studies also failed to show such a reduction, but the two trials were underpowered (12, 13). Although the results were not statistically significant, there were decreases in the intubation rate with heliox compared with air/O₂ in both trials, from 20 to 13% in the first study (12) and from 30 to 21% in the second trial (13). Of note, these studies used NIV only, not spontaneous heliox breathing between NIV sessions, and importantly, the duration of NIV sessions might have been insufficient. Also, the medical devices used in these studies were not specifically designed for heliox administration, which could have affected their performance (17). The present study was aimed at improving these limitations

by combining the beneficial physiological effects of continuous heliox administration during both NIV sessions and in between, using specifically adapted equipment, and ensuring sufficient duration of NIV (individual sessions and total daily use) and exposure to heliox (up to 72 hours). The main reason for the absence of observed benefit on outcome in the heliox group probably lies in the low NIV failure rate observed in both groups. One possible mechanism explaining the low intubation rate could be that some patients received uncontrolled oxygen therapy before ICU admission, thereby worsening initial hypercapnia and acidosis, a problem that can easily be corrected by adequate O₂ titration. The 14.5% failure rate in the air/O₂ group was much lower than the 25% rate used in designing the study, based on the two cited studies mentioned previously

(12, 13). Therefore, although the study could not show a benefit of heliox, this study also reflected the constant progress made by NIV in avoiding intubation for acute exacerbation of COPD in the ICU since the first prospective multicenter ICU study published 20 years ago (18). It remains to be seen whether any intervention can further reduce the NIV failure rate or if at some point there is an incompressible level of NIV failure. It is nonetheless possible that a subgroup of patients, which remains to be identified, might benefit from heliox.

In the subgroup of patients who required intubation, we found that the duration of invasive ventilation was significantly shorter in the heliox group, possibly in part due to less re-intubation. Though interesting, it was difficult to provide a clear explanation as to the

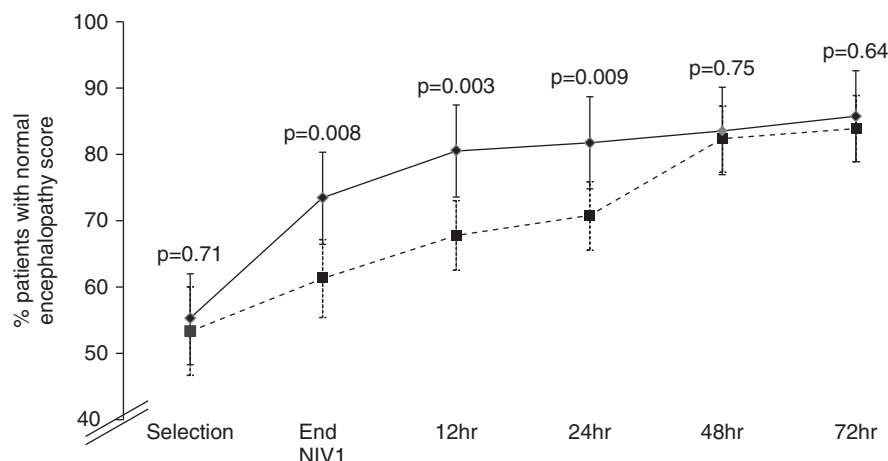


Figure 4. Encephalopathy score (intention-to-treat data set). Values are the percentage of patients ($\pm 95\%$ confidence intervals) with normal encephalopathy score. A statistical difference is seen post-treatment onset until 24 hours (χ^2). Helium/oxygen, solid lines; air/O₂, dashed lines. NIV = noninvasive ventilation.

underlying mechanisms involved. Although heliox was shown to reduce the WOB in intubated patients during weaning (19), no heliox was administered to our patients post-intubation. One hypothesis could be that because heliox reduces the WOB during NIV (9) and spontaneous breathing (8, 10) more than air/O₂, enhances oxygen delivery and use by muscles (20), and results in significantly improved physiological parameters, respiratory muscle fatigue was less pronounced. Consequently, even though invasive ventilation was required, weaning may have been facilitated. This would be particularly true for patients who required intubation

because of causes such as inability to clear secretions and atelectasis. Such a carryover effect of heliox is a possibility, but this finding should be interpreted with caution because our study was not designed to explore this point, which would warrant further pathophysiological investigation (20, 21).

From a physiological standpoint, although oxygenation was comparable in both groups during the treatment period, patients in the heliox group exhibited a significantly faster decrease in the respiratory rate during the first 12 hours, with a significant increase in pH and decrease in PaCO₂ from treatment onset until 72 hours. These results are in line with

those of previous short-term studies in smaller groups of patients (9, 11–13). Also, the encephalopathy score was markedly improved over the first 24 hours in all heliox patients compared with those of the air/O₂ group, a finding not previously reported. This is probably linked to the lower PaCO₂ levels and/or the lower WOB (22) found in patients who received heliox.

Some limitations of the study must be pointed out. First, the therapy was not blinded, due to various technical aspects, the most obvious being the voice alteration caused by He, which could not realistically be masked for up to 72 hours. Nonetheless, strict uniform criteria for initiating NIV and resorting to intubation were applied in all centers, and all criteria were reviewed by an independent adjudication committee. Second, although COPD with acute hypercapnic respiratory failure mandating NIV was the diagnostic entry criterion in the study, some degree of diagnostic or severity inhomogeneity is always possible. The study was conducted in intensive care, and the decision to include a patient and initiate treatment had to be made promptly; therefore, COPD was suspected in approximately one-half of the patients, but not confirmed at the time on inclusion because we used a pragmatic approach. Nonetheless, in the 205 patients for whom pulmonary function tests were collected, 80% presented with severe or very severe COPD. Also, the contribution of acute chronic heart failure could not be excluded as a contributing cause of acute respiratory failure, but the diagnosis of left ventricular dysfunction participating in the exacerbation is challenging at ICU admission.

No baseline differences were noted between groups (Table 1), and the main indicators of the type and severity of respiratory failure were in line with those of previous publications (12, 13). Duration of therapy could be considered a limitation. Heliox was administered during 72 hours, whereas the mean duration of NIV was 5 days, and approximately one-third of failures occurred after the end of the heliox administration (Figure 2B). Another potential limitation was the fact that a large number of patients were included in only a few centers. However, no difference was found when analyzing the results, which included only the large recruiters or the small recruiters. Also, there was no formal

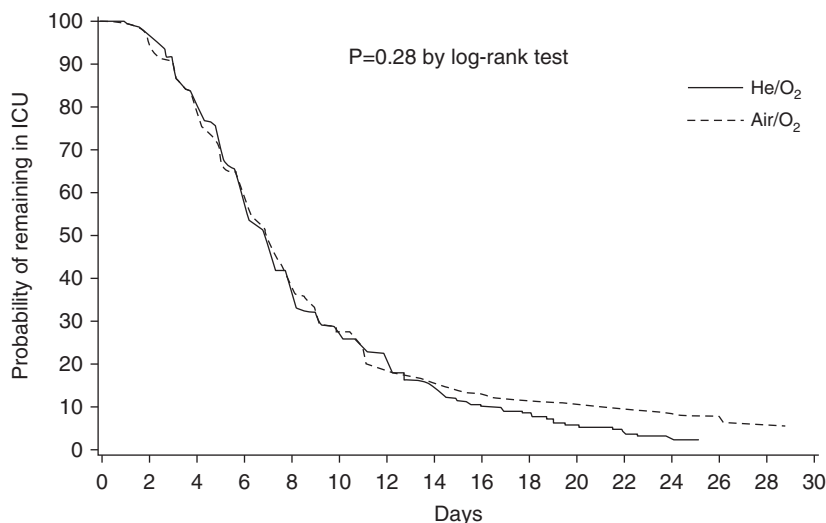


Figure 5. Probability of remaining in the intensive care unit (ICU) in the intention-to-treat set (n = 445).

Table 3. Safety by Study Groups

	Heliox (n = 225)	Air/O ₂ (n = 220)
AEs		
Patients with ≥1 AE, n (%)	136 (60.4)	129 (58.6)*
Patients with ≥1 serious AE, n (%)	89 (39.6)	83 (37.7) [†]
Total serious AEs, n	156	168
Serious AEs during study treatment, n	3	7
Serious AEs related to study drug, n	0	0
Tolerance during NIV sessions, n (%)		
Sessions prematurely stopped	146 (7.1)	232 (11.5)
Main reasons for ending		
Intolerance to facemask	85 (58.2)	150 (64.7)
Adverse event (including intubation)	27 (18.5)	39 (16.8)
Patient decision	9 (6.2)	18 (7.8)
Tolerance during ventilator-free sessions, n (%)		
Sessions prematurely stopped	143 (7.2)	61 (3.5)
Main reasons for ending		
Desaturation/hypoxemia	53 (37.1)	28 (45.9)
Other adverse event (including intubation)	48 (33.6)	29 (47.5)
Intolerance to facemask	15 (10.5)	1 (1.6)

Definition of abbreviations: AEs = adverse events; heliox = helium/oxygen; NIV = noninvasive ventilation.

*P = 0.70.

[†]P = 0.69, χ^2 test.

registry of how patients were approached and/or recruited, and how many did not meet their eligibility criteria or met their exclusion criteria. Finally, the study was stopped prematurely after a futility analysis because of the low event rate identified

by the committee. The initial power computation was based on an expected event rate of 25% and its reduction to 15% by heliox, which represents a 40% relative risk reduction. Of note, the study was designed 7 years ago, and the NIV failure

rate in the two studies available at the time in the air/O₂ group were 20% (12) and 30% (13), respectively.

In conclusion, in the largest study to date on severe acidotic COPD exacerbation in the ICU, a 72-hour heliox administration resulted in a significantly quicker improvement of respiratory acidosis, encephalopathy score, and respiratory rate, but it did not further reduce the NIV failure rate, which was already rather low (14.5%) with air/O₂. Future paths exploring the possible benefits of heliox in this setting could include better identification and selection of patients most likely to benefit, longer duration of treatment, and its timely cessation in the absence of rapid improvement. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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