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

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Abstract (249 words)

RATIONALE: During non-invasive ventilation (NIV) for COPD exacerbations, Helium/Oxygen (He/O_2) reduces work of breathing and hypercapnia more than Air/O_2 but impact on clinical outcome remains unknown.

OBJECTIVE: To determine whether continuous administration of He/O_2 for 72 hours, during and in-between NIV sessions, is superior to Air/O_2 in reducing NIV failure (25% to 15%) in severe hypercapnic COPD exacerbations.

METHODS: Prospective, randomized, open-label trial (16 intensive care units, 6 countries). Inclusion criteria: COPD exacerbations with $PaCO_2 \geq 45$ mmHg, $pH \leq 7.35$, and at least one: respiratory rate ≥ 25/min, $PaO_2 \leq 50$ mmHg, $SpO_2 \leq 90\%$. A 6-month follow-up was performed.

OUTCOMES: *Main:* NIV failure (intubation or death without intubation in ICU). *Secondaries:* physiological parameters, duration of ventilation, ICU and hospital stay, 6-month recurrence and rehospitalization rates.

MAIN RESULTS: Trial stopped prematurely (445 randomized patients) for a low global failure rate. NIV failure: Air/O_2 14.5% (N=32), He/O_2 14.7% (N=33, p=0.97). Time to NIV failure: He/O_2 group 93 hours (N=33), Air/O_2 group 52 hours (N=32, p=0.12). Respiratory rate, pH, $PaCO_2$ and encephalopathy score improved significantly faster with He/O_2. ICU stay was comparable between groups. In patients intubated after failing NIV, He/O_2 patients had a shorter ventilation duration (7.4±7.6 vs 13.6±12.6 d, p = 0.02) and ICU stay (15.8±10.9 vs 26.7±21.0 days, p = 0.01). No difference was observed in ICU and 6-month mortality.

CONCLUSIONS: He/O_2 improves respiratory acidosis, encephalopathy and respiratory rate more quickly than Air/O_2 but does not prevent NIV failure. Overall, the rate of NIV failure is low.

At a glance commentary

Scientific knowledge on the subject

During acute hypercapnic COPD exacerbation, inhaling a Helium/Oxygen (He/O_2) mixture has been shown to reduce airway resistance, $PaCO_2$, intrinsic PEEP and work of breathing more than Air/O_2 during both spontaneous breathing and non-invasive ventilation (NIV). However, the impact of He/O_2 on patient outcome remains unclear.

What this study adds to the field

In the largest study to date on acute COPD exacerbation requiring NIV in the ICU, using a protocolized duration of treatment with the gas mixtures, validated He/O_2 compatible equipment and strict pre-defined criteria for intubation, the overall failure rate with NIV is below 15%. The study shows that He/O_2 does not decrease the NIV failure rate, nor the length of stay in the ICU and hospital compared to Air/O_2. It has significant physiological effects allowing for a faster improvement.

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Introduction

Due to its ability to reduce the need for endotracheal intubation (ET) and mortality, non-invasive ventilation (NIV) has become a standard of care in acute exacerbation of chronic obstructive pulmonary disease (COPD) (1). Nonetheless, NIV fails to avoid ET in approximately 25% of patients (2, 3), who thereafter experience a longer ICU and hospital stay and 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 (He/O_2) mixture. Indeed, due its low density, He/O_2 reduces the resistance to flow in the airways, which in turn decreases the work of breathing (WOB) (4-7). In COPD, spontaneous breathing of He/O_2 decreases airway resistance to flow (8) and WOB (9), and a retrospective study documented a reduction of the intubation rate, hospital mortality and length of stay in the ICU in patients with acute exacerbation (10). Furthermore, during NIV, He/O_2 decreases $PaCO_2$ and dyspnea more than Air/O_2 (11), due to a reduction in airway resistance, intrinsic PEEP and work of breathing (9). However, two prospective randomized studies of NIV with He/O_2 have failed to show a reduction in the intubation rate and length of stay in the ICU (12, 13). Both studies, however, were underpowered and He/O_2 was applied only during NIV sessions, the duration of which might have been insufficient.

The purpose of this study was to explore whether the *continuous* inhalation of He/O_2 over 72 hours, using specific equipment, could reduce NIV failure, mortality and duration of ICU and hospital stays compared to the 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. Reference: ClinicalTrials.gov NCT01155310.

The study was conducted in compliance with Good Clinical Practice (GCP) 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, since inclusion needed to be made in the intensive care setting in patients with acute respiratory failure requiring 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 an uncompensated respiratory acidosis ($PaCO_2 \geq 45$ mmHg and arterial pH ≤ 7.35) on arterial blood gases drawn on room air or supplemental oxygen, and at least one of the following: respiratory rate ≥ 25 breaths per minute, partial pressure of oxygen in arterial blood (PaO_2) ≤ 50 mmHg, oxygen saturation (arterial - SaO_2 or pulse oximetry - SpO_2) $\leq 90\%$. Patients with severe pulmonary embolism, extensive pneumonia or pneumothorax were not to be included. Complete eligibility criteria are listed in the ESM (**Table 1e**). Of note, do-not-intubate (DNI) patients were not excluded, to better reflect "real-life" conditions since such patients might benefit from He/O_2 administration, which aims to avoid intubation, and because death was part of the main end-

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point and would capture the NIV failure. Eligible patients were randomly assigned by center to one of two study groups, receiving either He/O_2 or Air/O_2.

End-points

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

Delivery of treatment

During NIV, the gas mixtures were administered through an oro-nasal mask (Flexi Fit™ HC431, Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) with a Hamilton-G5 ventilator with Heliox option (Hamilton Medical AG, Bonaduz, Switzerland) (15), with either He/O_2 or Air/O_2, the first session starting 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 PEEP of 3 to 5 cm H_2O was used initially. He/O_2 78%/22% was manufactured by AIR LIQUIDE *Santé* FRANCE for the trial and was supplied in B50 gas cylinders pressurized at 200 bars. A minimum total of 6 hours of NIV were 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, He/O_2 was administered with a high-concentration oxygen facemask (Pulmanex® Hi-OX_{80}, Cardinal Health, Dublin OH, USA), using a specifically-

designed blender (Sentry He/O_2, Cardinal Health) (16). Patients in the Air/O_2 group received O_2 via the interface routinely in use in the center. The He/O_2 flow rate had to be adapted to the F_IO_2 (12 L/min for F_IO_2 from 0.22 to 0.35, and 15 L/min for F_IO_2 from 0.36 to 0.50). In the Air/O_2 group, O_2 titration was achieved by changes in the delivered O_2 flow rate. For both study groups, O_2 supplementation was titrated to maintain $SpO_2 \geq 90\%$. He/O_2 or Air/O_2 was to be administered for a maximum of 72 hours (study design, **Figure 1e**, ESM). Thereafter, patients in both groups received Air/O_2 according to clinical needs. Physiological variables and encephalopathy score (17) were followed closely for 72 hours. If intubation was required in the He/O_2 group patients, even within the 72 hours post-randomization, ventilation was performed with an Air/O_2 mixture. Therefore, He/O_2 was not administered to intubated patients.

There were no recommendations concerning supplemental oxygen, 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 non-blinded nature of the study: 1) the decision to intubate was based on the presence of at least 1 major or 2 minor published criteria (18), detailed in the ESM (**Table 1e**), and 2) an end-point adjudication and safety committee reviewed cases of NIV failure 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 had also the possibility of informing investigators of any methodology or safety issue and was allowed to propose holding or interrupting the study.

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Statistical analysis of clinical data collected

Study sample size estimation was based on a reduction in the NIV failure rate by He/O_2 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 2-sided tests performed was 0.05. No formal interim analyses were planned other than monitoring by the adjudication and safety committee (see above).

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 Chi-Square test and its calculation provided by SAS® version 9.3.

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

The Student's t-test was used to compare between study groups the cumulative duration of invasive ventilation in the subgroup of intubated patients, as well as the ICU lengths of stay in the subgroups of NIV failures and NIV successes separately. In these latter subgroups, time to ICU discharge (or time to death during index ICU stay) after randomisation was also described using survival methods and Kaplan-Meier's estimates and it 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 reported by the endpoint validation and safety committee, and a futility rule was applied (the likelihood of finding a significant difference based on the total observed event rate had to be lower than 30%), when a total of 445 patients were randomized over the 670 planned.

The study consort diagram is shown in **Figure 1**. 235 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 UK.

Table 1 outlines the baseline characteristics for both groups. COPD severity was assessable in 205 patients about 80% of those being GOLD 3 or 4 (**Table 2e**). Of note,35 patients had a pH > 7.35, whereas the inclusion criteria stipulate a pH ≤ 7.35. This is due to two reasons: a) 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; b) patients were selected on the entry criteria and it happened that a few patients improved between the time of enrollment and the first ABG after randomization. Eighty-four percent of the patients presented 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 (**Table 3e**). The main reason for the major protocol deviations was that the study treatment administration was not carried out according to the protocol for more than 50% of the treatment period, with this deviation occurring more frequently in the He/O_2 group compared to the Air/O_2 group (7.6% vs. 0.5%). NIV was started more than 120 minutes after randomization in five (2.2%) patients in the He/O_2 group and 6 (2.7%) patients in the Air/O_2 group. Detailed definition and full description of the PP

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population are provided in ESM **(Table 4e)**. Treatment administered for the acute episode is summarized in **Table 5e**. All the results are given in intention-to-treat (ITT) analysis.

Main End-Point: NIV failure

Table 2 summarizes the main outcomes. NIV failure rate was comparable between both groups (Air/O_2 32 patients - 14.5% [CI 10.2-19.9] vs. He/O_2 33 patients - 14.7% [CI 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/O_2 - 14.9% vs. He/O_2 – 15.1%, p = 0.96).

The mean±SD time to NIV failure was 92.8±128.4 hours in the He/O_2 group (n=33) and 51.5±74.7 hours in the Air/O_2 group (n=32)(p=0.12, t-test). **Figure 2A** shows the Kaplan-Meier analysis of the time to NIV failure, i.e., considering time of death or intubation for NIV-failure patients, and time to ICU discharge for NIV-success patients. **Figure 2B** represents, for NIV-failure patients, the time-frame of their intubation during their index ICU stay: most of the patients were intubated within the first 2 days, but the time to NIV failure seemed delayed in patients receiving He/O_2.

Criteria for intubation were comparable in the two groups (**Table 6e**).

The evaluation of possible predictors of NIV failure during the index ICU stay showed that baseline pH was the only significant factor ($p<0.0001$). Intubation rate was 34% when baseline pH was ≤ 7.25, 10% if pH was > 7.25 but ≤ 7.35, and 3% if pH was > 7.35and this rate was not influenced by the gas mixture received.

Physiological effects

The time-course of the main physiological variables is summarized in **Figures 3 and 4**. In the He/O_2 group, respiratory rate decreased significantly quicker during the first 12 hours, while pH was increased and $PaCO_2$ decreased significantly more post-treatment onset until 72

hours. Pulse oximetry revealed no difference in oxygenation between groups. **Figure 4** shows that the proportion of patients who normalized their encephalopathy score was significantly higher during the first 48 hours in patients receiving He/O_2.

NIV Failure patients

Although ICU LOS was similar in both study groups (**Figure 5, Table 2**), probability of prolonged ICU stay was higher in Air/O_2 patients failing NIV (Air/O_2 26.7 ± 21.0, n=32 vs. He/O_2 15.8 ± 10.9 d, n=33, p = 0.01, Log rank) (**Figure 3e, Table 2**). When NIV failure resulted in intubation (n=63), duration of invasive ventilation was also significantly higher in the Air/O_2 group (Air/O_2 13.6 ± 12.6 d, n=32 vs He/O_2 7.4 ± 7.6 d, n=31, p = 0.02, Student's t-test)(**Table 2**). Reintubation occurred in 8 of the 32 Air/O_2 group patients (25.0%) and 4 of the 31 He/O_2 group patients (12.9%). All 8 re-intubated Air/O_2 group patients died in ICU or during the 6-mo follow-up whether it was the case for 2 of the 4 re-intubated He/O_2 group patients. Lastly, in patients with NIV failure, 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 7e**. No difference was documented between the two groups.

Administration of both gas mixtures was well tolerated: 7.1% of He/O_2 NIV sessions and 11.5% of Air/O_2 NIV sessions had to be discontinued, mainly because of mask intolerance, intubation, adverse event and patient willingness. He/O_2 and Air/O_2 ventilator-free administration had to be discontinued in 7.2% and 3.5% of sessions, respectively (**Table 3**).

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The mean He/O_2 consumption per patient was 37.2±18.6 kL, corresponding to about 4±2 B50 per patient for the 72-hr treatment.

6-month follow-up

No difference was noted between gas mixtures for 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 He/O_2 group, and 22 patients (10%) of the Air/O_2 group were re-admitted in 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 He/O_2 group and 6 patients (2.7%) of the Air/O_2 group required invasive ventilation.

Discussion

The present study, which included 445 patients, is the largest to date on acute COPD exacerbation requiring NIV in the ICU with a 6-month follow-up. It is also the largest study on the medical use of He/O_2 and the first to assess its continuous administration for up to 72 hours. Its main strengths are the number of patients, the continuous He/O_2 administration, the protocolized duration of treatment with the gas mixtures, the use of validated He/O_2 compatible equipment, of strict pre-defined criteria for intubation, and the 6-month follow-up. While confirming the favorable physiological effects of He/O_2, 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 to Air/O_2. Although dealing with small numbers and subgroup analyses, both requiring great caution in their

interpretation, the duration of mechanical ventilation and the ICU LOS were significantly shorter in the subgroup of patients having received He/O_2 and in whom NIV failed.

The main finding of our study is that inhalation of He/O_2 for up to 72 hours, during both NIV and spontaneous breathing, did not reduce the intubation rate in a population of COPD patients with acute exacerbation. 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 intubation rate with He/O_2 compared to Air/O_2 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 He/O_2 breathing between NIV sessions, and, importantly, the duration of NIV sessions may have been insufficient. Also, the medical devices used in these studies were not specifically designed for He/O_2 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 He/O_2 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 He/O_2 (up to 72 hours). The main reason for the absence of observed benefit on outcome in the He/O_2 probably lies in the very low NIV failure rate now observed in both groups. One possible mechanism explaining the low intubation rate could be that some patients had received uncontrolled oxygen therapy prior to ICU admission, thereby worsening initial hypercapnia and acidosis, a problem that can easily be corrected by adequate O_2 titration. The 14.5% failure rate in the Air/O_2 group was much lower than the 25% rate used in designing the study, based on the two cited studies mentioned above (12, 13). Therefore, although the study could not show a benefit of He/O_2, this study also reflects the

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constant progress made by NIV in avoiding intubation for acute exacerbation of COPD in the ICU, since the first prospective multicentre 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 He/O_2.

In the subgroup of patients requiring intubation, we found that the duration of invasive ventilation was significantly shorter in the He/O_2 group, possibly in part due to less re-intubation. Though interesting, it is difficult to provide a clear explanation as to the underlying mechanisms involved. Indeed, even though He/O_2 has been shown to reduce the WOB in intubated patients during weaning (19), no He/O_2 was administered to our patients post-intubation. One could hypothesize that, since He/O_2 reduces the WOB during NIV (9) and spontaneous breathing (8, 10) more than Air/O_2, enhances oxygen delivery and utilization by muscles (20), and resulted in significantly improved physiological parameters, respiratory muscle fatigue was less pronounced, even though invasive ventilation was required, and therefore weaning was 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 He/O_2 is a possibility, but this finding should be interpreted with caution since our study was not designed to explore this point, which would warrant further pathophysiological investigation (20, 21).

From a physiological standpoint, whereas oxygenation was comparable in both groups during the treatment period, patients in the He/O_2 group exhibited a significantly quicker decrease in respiratory rate during the first 12 hours, with a significant increase in pH and decrease in $PaCO_2$ 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 He/O_2 patients compared to those of the Air/O_2 group, a finding not previously reported. This is probably linked to the lower $PaCO_2$ levels and/or the lower WOB (22) found in patients receiving He/O_2.

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, which cannot realistically be masked for up to 72 hours. Nonetheless, in all centers strict uniform criteria for initiating NIV and resorting to intubation were applied, all criteria being 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. Indeed, the study was conducted in intensive care, the decision to include a patient and initiate treatment had to be taken promptly, therefore in about half of the patients COPD was suspected, not confirmed at the time on inclusion as we used a pragmatic approach. Nonetheless, in the 205 patients for whom pulmonary function tests were collected, 80% presented severe or very severe COPD. Also, the contribution of acute on chronic heart failure cannot be excluded as a contributing cause of ARF but the diagnosis of left ventricular dysfunction participating to the exacerbation is very 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 as a limitation. He/O_2 was administered during 72 hours whereas the mean duration of NIV was 5 days and about one third of failures occurred after the end of the He/O_2 administration (**Figure 2B**). Another potential limitation is the fact that a large number of patients were included in only a few centers. However, no

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difference was found when analyzing the results including only the large recruiters or the small recruiters. Also, there was no formal registry of how patients were approached/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 due the low event rate identified by the committee. Indeed, the initial power computation was based on an expected event rate of 25% and its reduction to 15% by He/O_2, 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/O_2 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-hr He/O_2 administration resulted in a significantly quicker improvement of respiratory acidosis, encephalopathy score and respiratory rate, but did not further reduce NIV failure rate, already rather low (14.5%) with Air/O_2. Possible future paths exploring the possible benefits of He/O_2 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.

Role of the Funder/Sponsor: Air Liquide Healthcare, in collaboration with the academic clinical investigators, provided input on the design and conduct of the study; oversaw the collection, management, and statistical analysis of data; and contributed to the interpretation of the data and the preparation, review, and submission of the manuscript. The final decision on manuscript submission was made by the authors; the sponsor did not have the right to veto or require publication.

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Figure legends

***Figure 1*:** Consort diagram of the study.

Of note, one patient allocated to receive He/O_2 group was intubated few minutes after randomisation and did not receive He/O_2 but completed the study.

***Figure 2**:* **A.** Survival analysis of the time to NIV failure (ITT data set). The analysis considers time to NIV failure as the time of occurrence of the NIV failure, whether NIV-success patients are censored at the time of index 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. He/O_2 full lines, Air/O_2 dashed lines. Time to NIV failure was 93±128 hours in the He/O_2 group (N=33) and 52±75 hours in the Air/O2 group (N=32), *p=0.12 (t-test)*

Figure 3: Physiological outcomes (ITT data set). **A.** Respiratory rate (RR): a statistical difference is seen post-treatment onset until 12 hours (t-test). **B.** pH and **C.** $PaCO_2$: overall treatment effect: $p<0.0001$ at all time points (ANCOVA). Absolute differences are shown in mmHg for $PaCO_2$. **D.** SpO_2 (room air or supplemental O_2): no difference is seen for SpO_2, at all time points. He/O_2 full lines, Air/O_2 dashed lines. Values are mean ± 95% confidence intervals for RR, pH and $PaCO_2$; mean + SD for SpO_2.

Figure 4: Encephalopathy score (ITT data set). Values are % patients (± 95% confidence intervals) with normal encephalopathy score. A statistical difference is seen post-treatment onset until 24 hours (chi-2). He/O_2 full lines, Air/O_2 dashed lines.

***Figure 5**:* Probability of remaining in the ICU in the ITT set (n=445). He/O_2 full lines, Air/O_2 dashed lines.

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Tables

Table 1: Baseline characteristics for the ITT data set. Values are mean ± SD or number (n), % of patients. *Abbrev: PFTs: pulmonary function tests; FEV1: forced expiratory volume in one second.*

	He/O_2 (n=225)	**Air/O_2** (n=220)	**All** (n=445)
Demographics and study disease characteristics			
Age -years	68.9 ± 11.4	66.9 ± 11.4	67.9 ± 11.4
Gender (M/W) – n	149 / 76	158 / 62	307 / 138
BMI - Kg/m^2	25.7 ± 5.5	25.9 ± 6.3	25.8 ± 5.9
BMI ≤ 20 - n (%)	36 (16)	34 (16)	70 (16)
BMI > 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)
FEV1 - %predicted value	36 ± 14	35 ± 15	36 ± 15
Stable $PaCO_2$ - mmHg	48 ± 9	49 ± 10	49 ± 10
Prior ICU admission			
Admission in ICU in the last 12 months - n (%)	35 (16)	27 (12)	62 (14)
Intubated in the last 12 months - n (%)	8 (4)	6 (3)	14 (3)
Characterisation 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 (0-217)	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 - b/min	29.3 ± 6.8	28.8 ± 5.4	29.0 ± 6.1
PaO_2 – mmHg	76.9 ± 36.7	73.2 ± 34.7	75.1 ± 35.8
$PaCO_2$ – mmHg	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 prior inclusion - n (%)	113 (50)	111 (50)	224 (50)
Do Not Intubate – no. (%)	3 (1.3%)	5 (2.3%)	8 (1.8%)

Table 2: Main outcomes for the ITT data set and the ITT subgroups of NIV failure or success. Values are mean ± SD or number (n), % of patients.* Pearson's Chi-2; [#] Student's t-test; [&]log-rank; [+]Fisher's exact test

ITT data set	**He/O_2** (n=225)	**Air/O_2** (n=220)	**p**
NIV failure - n (%)	33 (14.7)	32 (14.5)	0.97*
Intubation - n (%)	31 (13.8)	32 (14.5)	0.82*
NIV duration - days	5.3 ± 4.2	5.1 ± 4.6	0.69[#]
First 24 hrs, hours	14.3 ± 6.1	13.9 ± 5.4	0.53[#]
From 24th to 48th hr, hours	10.6 ± 4.6	10.4 ± 4.9	0.77[#]
From 48th to 72th hr, hours	9.8 ± 4.3	9.2 ± 4.1	0.27[#]
Length of stay - days			
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-month	40 (17.8)	35 (15.9)	0.60*
ITT data set – subgroup of NIV failure	**He/O_2** (n=33)	**Air/O_2** (n=32)	**p**
Duration of ventilation - days			
IV	7.4 ± 7.6	13.6 ± 12.6	*0.02*[#]
Total NIV prior IV + IV	10.8 ± 8.9	16.0 ± 12.3	0.06[#]
Length of stay - days			
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-month	14 (42.5)	15 (46.8)	0.72*
ITT data set – subgroup of NIV success	**He/O_2** (n=192)	**Air/O_2** (n=188)	**p**
NIV duration - days	5.5 ± 4.1	5.6 ± 4.6	0.87[#]
Length of stay - days			
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-month	26 (13.5)	20 (10.6)	0.39*

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Table 3: Safety by study groups. * p=0.70 and **p=0.69, Chi-square test.

	He/O_2 (n=225)	**Air/O_2 (n=220)**
Adverse events (AE)		
n (%) patients with ≥ 1 AE	136 (60.4)	129 (58.6)*
n (%) patients with ≥ 1 serious AE	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 of sessions prematurely stopped (%total)	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 of sessions prematurely stopped (%total)	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)*

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Figure 1

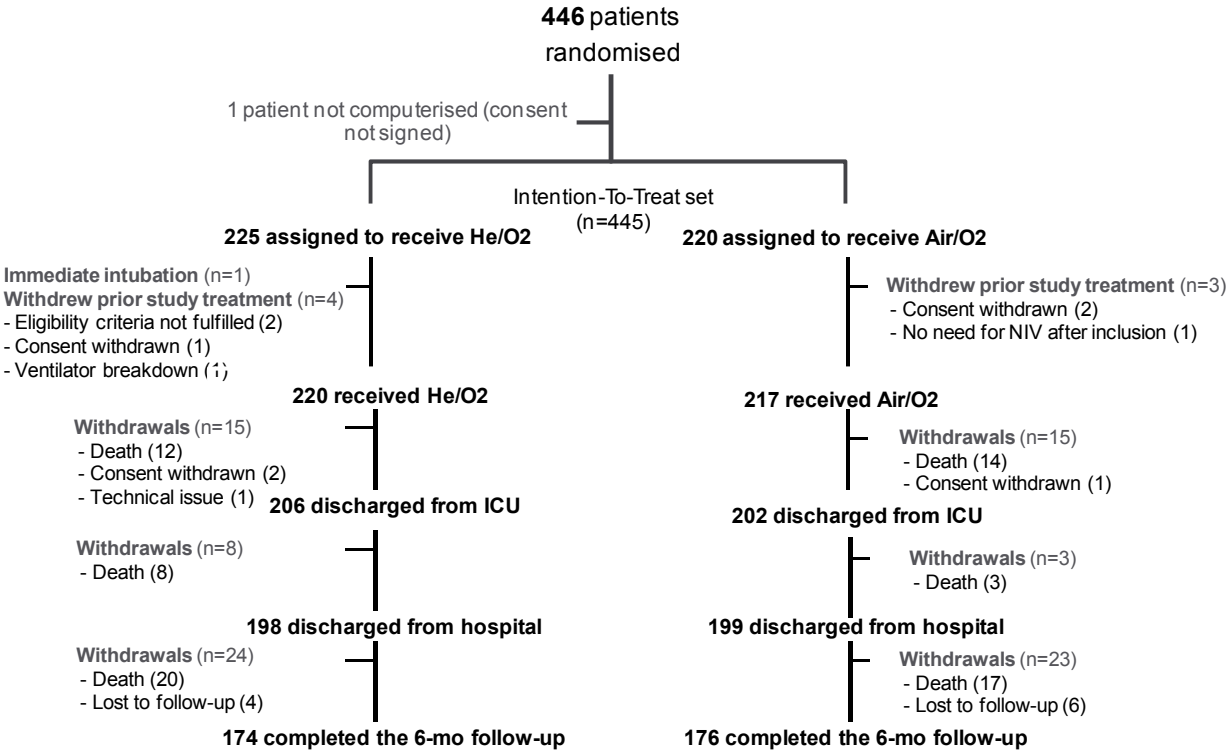
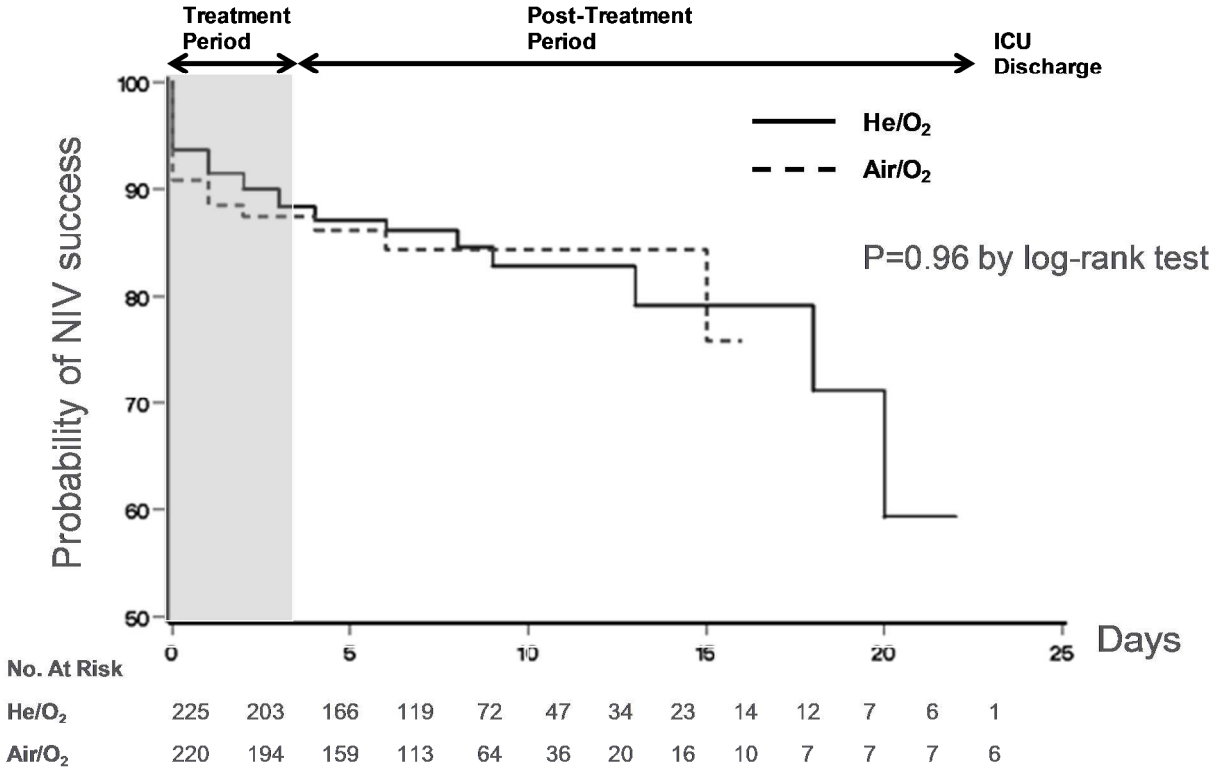


Figure 2 A



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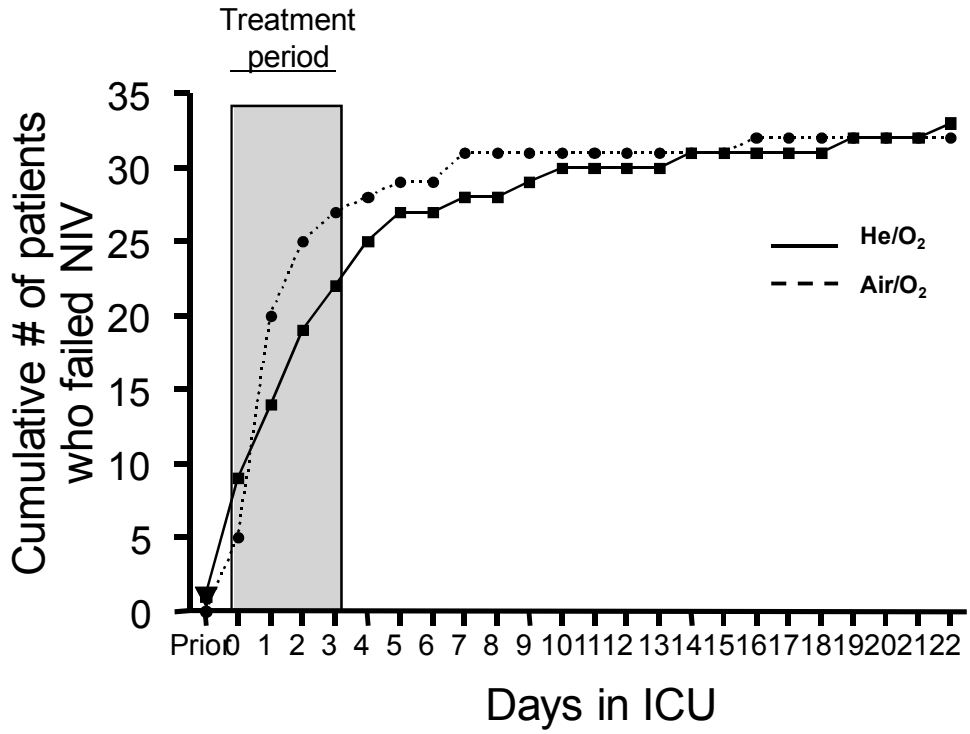

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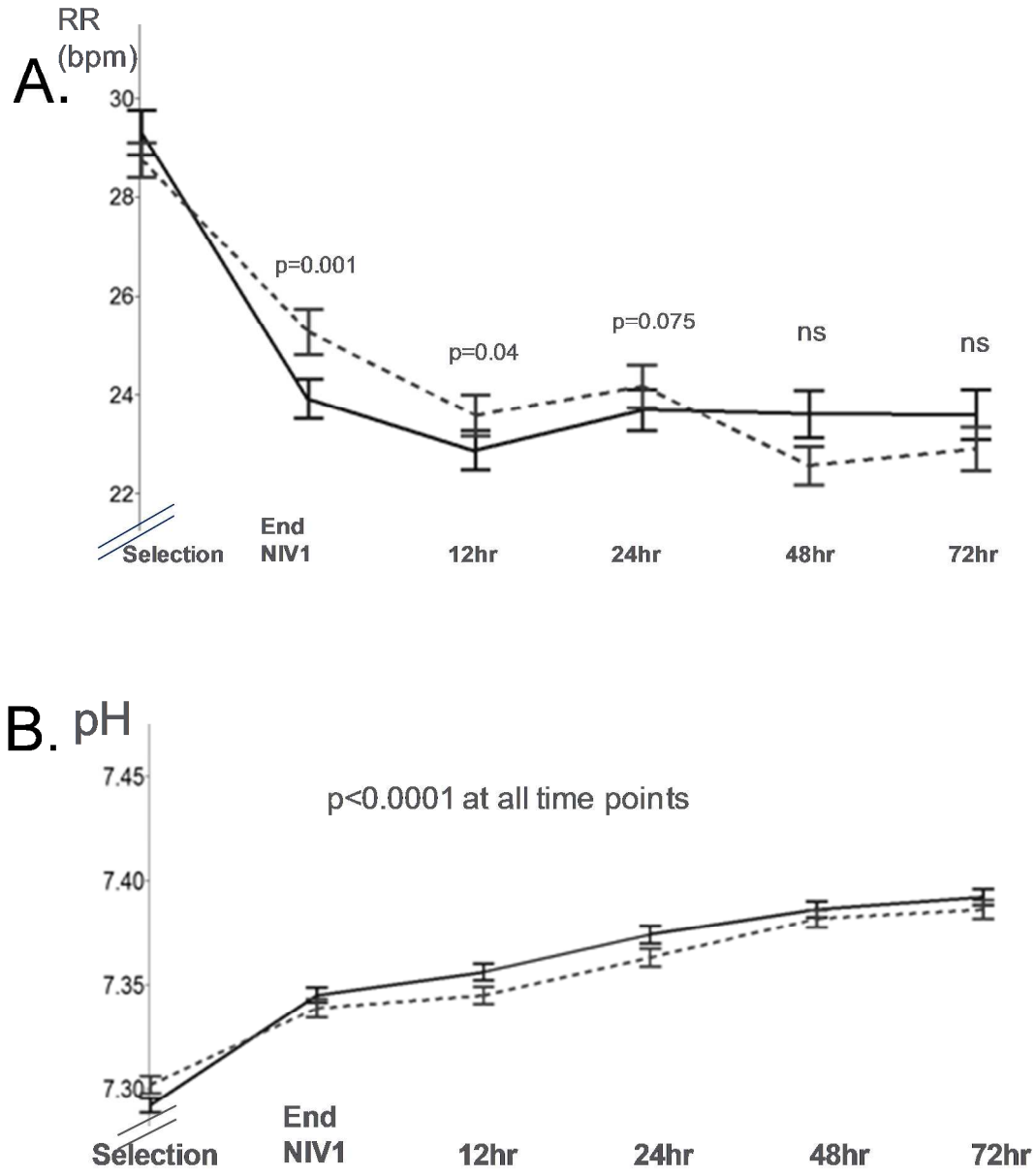
Figure 3



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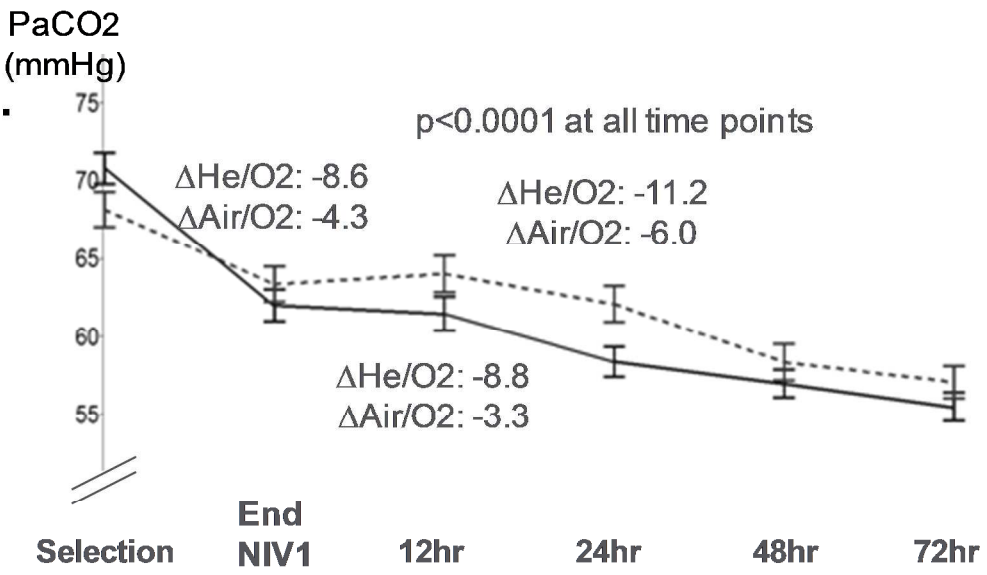

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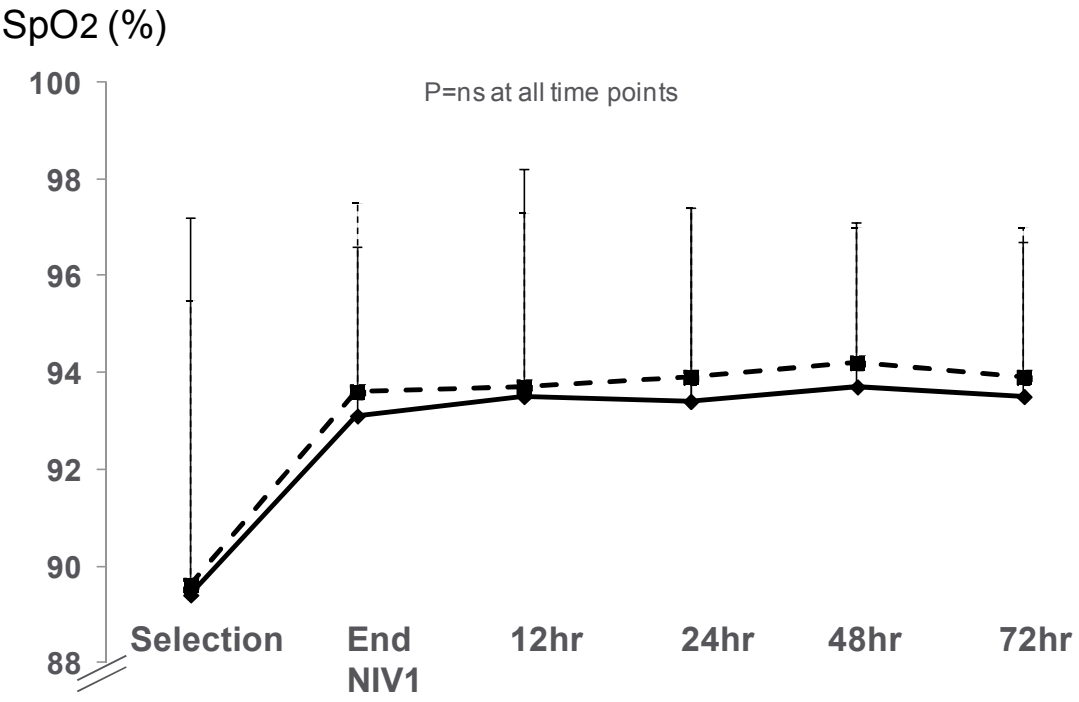

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Figure 4

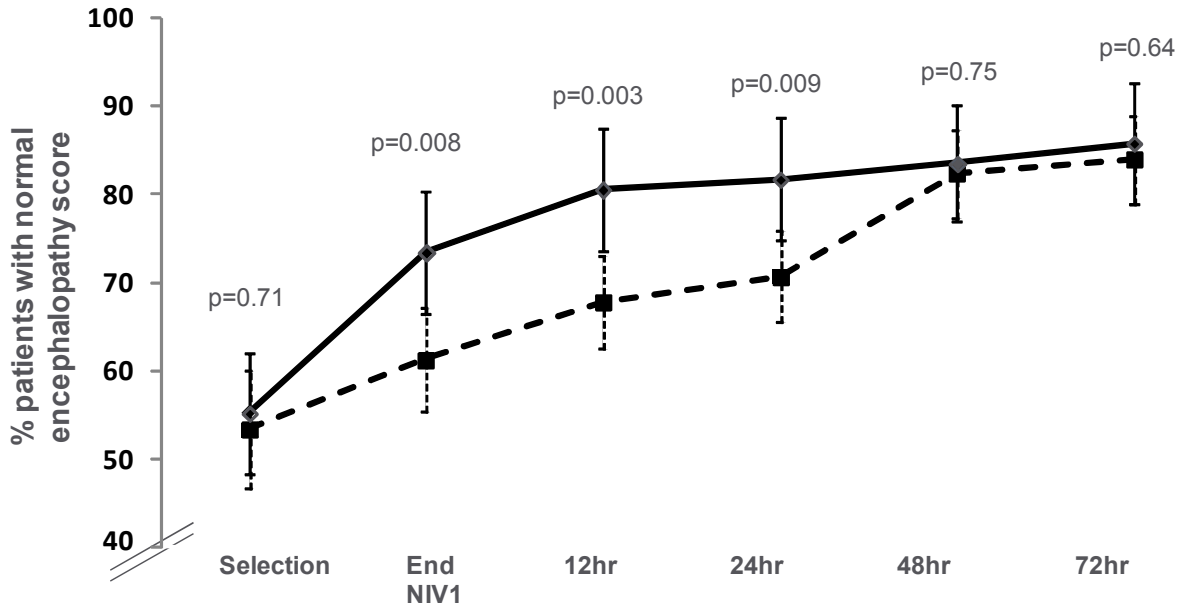
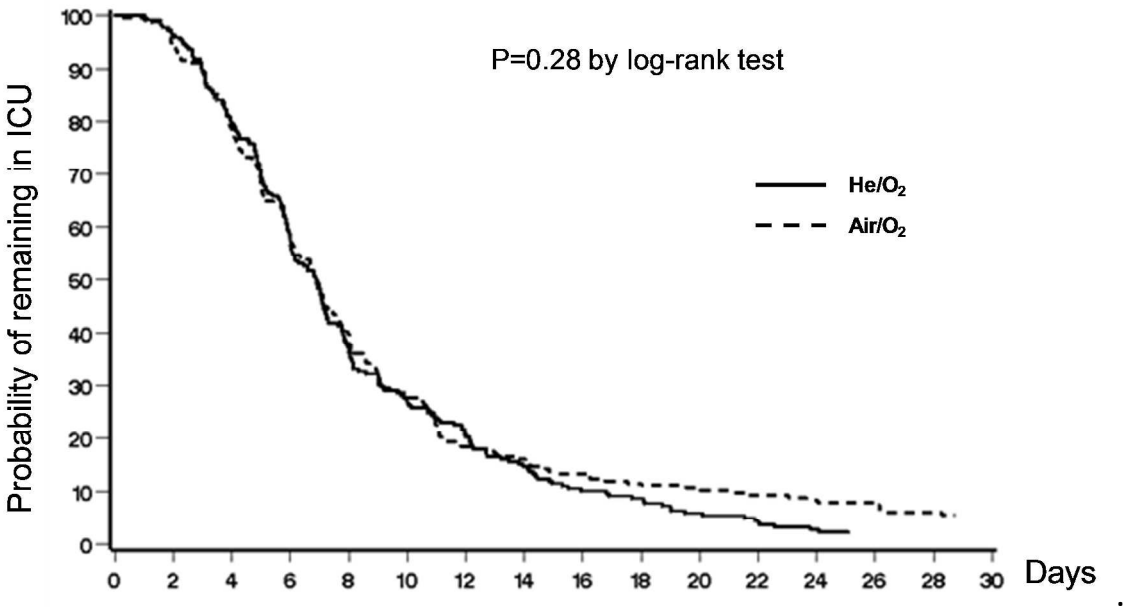


Figure 5

A.



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Online Supplement

ESM Tables and figures

Design and Methods

Table 1e: Complete list of inclusion /exclusion/intubation criteria.

Inclusion criteria
1. Male or female patient, aged ≥ 35 years,
2. Patient with known or suspected COPD,
3. Patient presenting current exacerbation of COPD with hypercapnic acute respiratory failure,
4. Patient presenting the following criteria for starting NIV sessions: *4.a)* $PaCO_2$ ≥ 45 mmHg *(6.0 kPa),* AND arterial pH ≤ 7.35, and at least 1 of the following: *4.b)* Respiration rate ≥ 25 breaths per minute, or *4.c)* PaO_2 ≤ 50 mmHg *(6.7 kPa)* or SaO_2 ≤ 90% or SpO_2 ≤ 90%,
5. Patient admitted in an Intensive Care Unit or an Intermediate Care Unit (ICU),
6. Written informed consent signed and dated by the patient or next of kin after full explanation of the study by the investigator prior to participation.
Exclusion criteria
1. Patient previously randomised in the study,
2. Patient admitted in the ICU for more than 24 hours and/or having received NIV in ICU for more than 6 hours *(in total)* for the current exacerbation of COPD,
3. Patient with tracheostomy,
4. Patient who had lung transplant,
5. Patient having a contraindication to NIV: *5.a)* Respiratory arrest, severe acute respiratory failure with high probability of imminent intubation, *5.b)* Sustained haemodynamic instability *(hypotension with systolic blood pressure < 90 mmHg despite volume loading and/or administration of vasopressor treatment),* *5.c)* Coma, impaired consciousness, uncooperative patient, neurologic instability not due to acute hypercapnia *(e.g., stroke, substance abuse or withdrawal, ...),* *5.d)* Shock or multiple organ failure syndrome, *5.e)* Severe ventricular rhythm disorders,

5.f) Uncontrollable vomiting,

5.g) Recent facial or gastro-oesophageal surgery, severe craniofacial trauma,

6. Patient requiring oxygen flow rate > 6 L/min or F_IO_2 > 0.50,
7. Patient with acute respiratory failure believed to be attributable to a current significant chronic disease other than COPD *(asthma, significant bronchiectasis, cystic fibrosis, sarcoidosis, lung fibrosis, kyphoskoliosis, neuromuscular disease, …)*, or to severe pulmonary embolism, extensive pneumonia or pneumothorax *(either currently documented and not drained at selection or recent episode < 1 month),*
8. Patient with severe concomitant chronic systemic disease with a limited probability of survival (< 6 months),
9. Pregnant or lactating woman,
10. Patient with known or suspected allergy to facemask compounds,
11. Patient who has received another investigational drug within 30 days prior to selection.

Intubation criteria

Major criteria:

1. Respiratory arrest
2. Respiratory pauses with loss of consciousness or gasping for air
3. Psychomotor agitation making nursing care impossible and requiring deep sedation;
4. Sustained bradycardia (heart rate < 50 beats per minute with loss of alertness)
5. Sustained haemodynamic instability with systolic blood pressure < 70 mmHg

Minor criteria:

1. Respiration rate > 35 breaths per minute and above its value at Selection
2. Arterial pH value < 7.30 and below its value at Selection
3. PaO_2 < 45 mmHg (6.0 kPa) despite oxygen therapy (up to 5 L/min)
4. Increase of the encephalopathy score.

Intubation was decided in the presence of at least one major criterion or two minor criteria.

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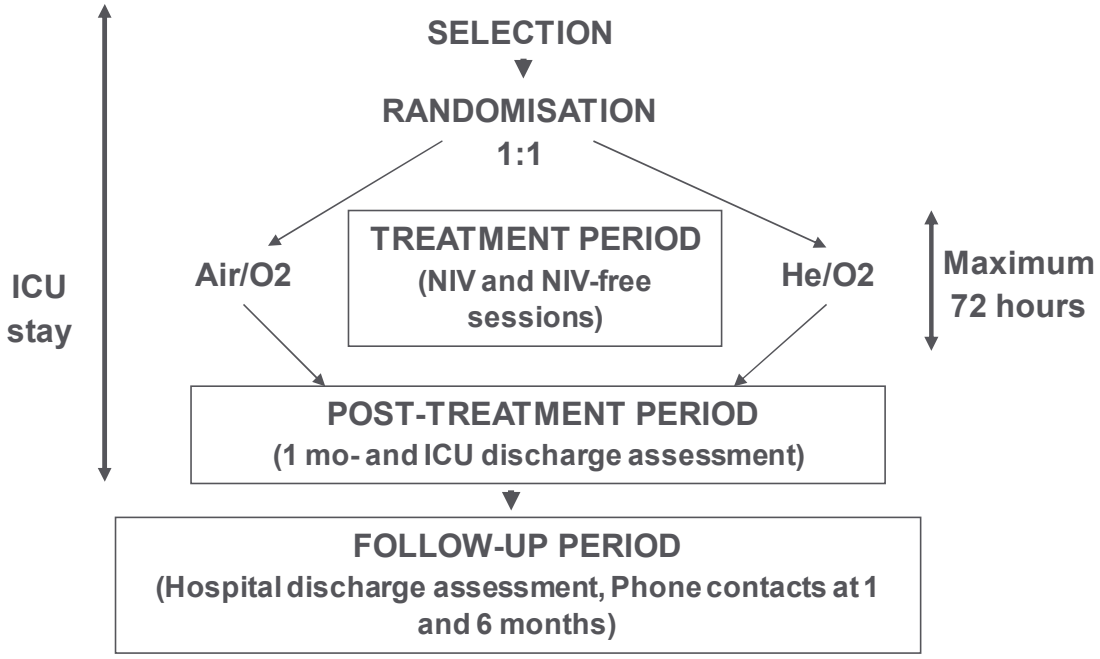
Figure 1e: Study design.



Results

Table 2e. Baseline characterisation of COPD and comorbidities. Most common comorbidities (reported in 5% or more of patients) by MedDRA System Organ Class and Preferred Term.

	He/O_2 (n=225)	**Air/O_2 (n=220)**	**All (n=445)**
GOLD COPD severity assessment	**n=111**	**n=94**	**n=205**
2	12 (10.8%)	8 (8.5%)	20 (9.8%)
3	55 (49.5%)	31 (33.0%)	86 (42.0%)
4	34 (30.6%)	44 (46.8%)	78 (38.0%)
FEV_1/FVC>70% or FEV1≥80%	10 (9.0%)	11 (11.7%)	21 (10.2%)
Most recent stable arterial blood gases	**n=95**	**n=85**	**n=180**
PaO_2 - mmHg	66.8 ± 13.5	64.5 ± 11.0	65.7 ± 12.4
$PaCO_2$ - mmHg	48.0 ± 9.5	49.5 ± 9.9	48.7 ± 9.7
Patients with $PaCO_2$>52 mmHg – n (%)	26 (27.4%)	29 (34.1%)	55 (30.6%)
$HCO3^-$ - mmol/L	30.4 ± 4.7	30.8 ± 5.7	30.5 ± 5.1
Exacerbations in the previous 12 months			
Patients with at least 1	110 (46.3%)	92 (39.6%)	202 (43.0%)
Patients with at least 1 hospitalized	77 (34.2%)	61 (27.7%)	138 (31.0%)
COPD medication prior admission			
Inhaled beta-2 agonists	51 (22.7%)	55 (25.0%)	106 (23.8%)
Inhaled anticholinergics	42 (18.7%)	44 (20.0%)	86 (19.3%)
Inhaled corticosteroids	3 (1.5%)	3 (1.4%)	6 (1.4%)
Home noninvasive ventilation	5 (2.2%)	4 (1.8%)	9 (2.0%)
Home oxygen	11 (4.9 %)	9 (4.1 %)	20 (4.5%)
Comorbidities			
Patients with at least 1 comorbidity – n (%)	192 (85.3%)	182 (82.7%)	374 (84.0%)
Most common comorbidities			
Vascular disorders	**122 (54.2%)**	**109 (49.5%)**	**231 (51.9%)**
Hypertension	116 (51.6%)	106 (48.2%)	222 (49.9%)
Cardiac disorders	**92 (40.9%)**	**82 (37.3%)**	**174 (39.1%)**
Atrial fibrillation	30 (13.3%)	24 (10.9%)	54 (12.1%)
Ischemic cardiomyopathy	20 (8.9%)	21 (9.5%)	41 (9.2%)
Diastolic dysfunction	18 (8.0%)	12 (5.5%)	30 (6.7%)
Metabolism and nutrition disorders	**70 (31.1%)**	**71 (32.3%)**	**141 (31.7%)**
Diabetes	50 (22.2%)	41 (18.7%)	91 (40.9%)
Dyslipidaemia	17 (7.6%)	26 (11.8%)	43 (9.7%)
Respiratory, thoracic and mediastinal disorders	**36 (16.0%)**	**46 (20.9%)**	**82 (18.4%)**
Sleep apnea syndrome	15 (6.7%)	17 (7.7%)	32 (7.2%)
Psychiatric disorders	**36 (16.0%)**	**29 (13.2%)**	**65 (14.6%)**
Depression	17 (7.6%)	14 (6.4%)	31 (7.0%)
Renal and urinary disorders	**15 (6.7%)**	**14 (6.4%)**	**29 (6.5%)**
Endocrine disorders	**14 (6.2%)**	**14 (6.4%)**	**28 (6.3%)**
Hypothyroidism	12 (5.3%)	12 (5.5%)	24 (5.4%)
Gastrointestinal disorders	**12 (5.3%)**	**15 (6.8%)**	**27 (6.1%)**
Neoplasms benign, malignant and unspecified	**12 (5.3%)**	**11 (5.0%)**	**23 (5.2%)**

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Table 3e. Major protocol deviations in the 31 patients excluded from the PP data set.

	He/O_2 (n=225)	Air/O_2 (n=220)	Total (n=445)
Patient with at least 1 major deviation, n (%)	26 (11.6)	5 (2.3)	31 (7.0)
Type of Major Deviations, n (%)			
Never treated	5 (2.2)	3 (1.4)	8 (1.8)
No known or suspected COPD	1 (0.4)	0 (0.0)	1 (0.2)
No current COPD exacerbation at ICU admission	2 (0.9)	0 (0.0)	2 (0.4)
Acute respiratory failure due to chronic disease other than COPD	2 (0.9)	0 (0.0)	2 (0.4)
Physiological criteria not fulfilled for starting NIV	2 (0.9)	1 (0.5)	3 (0.7)
Study treatment administration not Per Protocol more than 50% of the overall treatment period	17 (7.6)	1 (0.5)	18 (4.0)

Table 4e. Baseline characteristics in the PP data set. Values are mean ± SD or number (n), % of patients. *Abbrev: PFTs: pulmonary function tests; FEV1: forced expiratory volume in one second.*

	He/O_2 (n=199)	**Air/O_2** (n=215)	**All** (n=414)
Demographics and study disease characteristics			
Age -years	69.3 ± 11.3	66.7 ± 11.4	68.0 ± 11.4
Gender (M/W) – n	133 / 66	156 / 59	289 / 125
BMI - Kg/m^2	25.9 ± 5.4	26.0 ± 6.3	26.0 ± 5.9
BMI ≤ 20 - n (%)	29 (15)	33 (16)	62 (15)
BMI > 30 - n (%)	46 (23)	50 (24)	96 (23)
Smoking status			
Current smokers - n (%)	73 (37)	93 (43)	166 (40)
Ex-smokers - n (%)	101 (51)	104 (48)	205 (50)
Pack-years	56 ± 28	61 ± 30	59 ± 29
Lung function			
Available PFTs - n (%)	113 (57)	103 (48)	216 (52)
FEV1 - %predicted value	37 ± 14	35 ± 16	36 ± 15
Stable $PaCO_2$ - mmHg	48 ± 9	50 ± 10	49 ± 9
Prior ICU admission			
Admission in ICU in the last 12 months - n (%)	30 (15)	27 (13)	57 (14)
Intubated in the last 12 months - n (%)	8 (4)	6 (3)	14 (3)
Characterisation of the COPD exacerbation episode			
Main provenance			
Emergency room – n (%)	154 (77)	166 (77)	320 (77)
Medical ward – n (%)	19 (9.5)	28 (13)	47 (11)
Home – n (%)	21 (11)	15 (7)	36 (9)
Other – n (%)	5 (2.5)	6 (3)	11 (3)
Simplified Acute Physiology Score III (0-217)	49.9 ± 7.8	48.7 ± 7.6	49.3 ± 7.7
Main causes of COPD exacerbation			
Infection – n (%)	106 (53)	113 (53)	219 (53)
Undetermined – n (%)	43 (22)	51 (24)	94 (23)
Cardiac – n (%)	32 (16)	30 (14)	62 (15)
Respiratory rate - b/min	29.4 ± 6.9	28.8 ± 5.4	29.1 ± 6.1
PaO_2 – mmHg	77.6 ± 38.3	72.5 ± 33.3	74.9 ± 35.9
$PaCO_2$ – mmHg	70.6 ± 15.9	68.0 ± 16.8	69.2 ± 16.4
pH	7.29 ± 0.05	7.30 ± 0.06	7.30 ± 0.06
Patients having received NIV prior inclusion - n (%)	106 (53)	108 (50)	214 (52)

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Table 5e. Treatment of the COPD exacerbation episode. Most common medication (reported in 10% or more of patients), by WHO-Drug ATC2 code, started during the treatment period. Characteristics of NIV during the treatment period (values are mean±standard deviation).

	He/O_2 (n=225)	**Air/O_2** (n=220)	**All** (n=445)
Medication received			
Antithrombotic agents	180 (80.0%)	182 (82.7%)	362 (81.3%)
Drugs for obstructive airway diseases	138 (61.3%)	148 (67.3%)	286 (64.3%)
Drugs for acid-related disorders	90 (40.0%)	94 (42.7%)	184 (41.3%)
Systemic antibiotics	93 (41.3%)	88 (40.0%)	181 (40.7%)
Diuretics	62 (27.6%)	61 (27.7%)	123 (27.6%)
Systemic corticosteroids	56 (24.9%)	56 (25.5%)	112 (25.2%)
Psycholeptics	47 (20.9%)	50 (22.7%)	97 (21.8%)
Cardiac therapy	38 (16.9%)	44 (20.0%)	82 (18.4%)
Drugs used in diabetes	25 (11.1%)	42 (19.1%)	67 (15.1%)
Calcium channel blockers	37 (16.4%)	27 (12.3%)	64 (14.4%)
Analgesics	28 (12.4%)	22 (10.0%)	50 (11.2%)
NIV treatment			
Duration of the first NIV session – hours	4.04 ± 3.20	3.73 ± 2.94	3.88 ± 3.07
NIV sessions during the treatment period - n	9.8 ± 3.8	9.8 ± 3.7	9.8 ± 3.8
Pressure support – cmH_2O	13.7 ± 3.5	14.2 ± 3.3	13.9 ± 3.5
PEEP – cmH_2O	5.0 ± 1.2	5.2 ± 1.3	5.1 ± 1.3

Table 6e. Criteria which led to endotracheal intubation by study groups. ITT population. Results are presented as no. (%). Not statistically significant difference between both groups for all variables. *Abbrev:* HR: heart rate; RR: respiratory rate; SBP: systolic blood pressure.

	He/O_2 (n=31)	**Air/O_2 (n=32)**
Patients with ≥1 major criterion	10 (32.3%)	13 (40.6%)
Patients with ≥2 minor criteria	19 (61.3%)	14 (43.8%)
Patients with 0 or 1 minor criteria	2 (6.5%)	5 (15.6%)
Presence of major criteria		
• Respiratory arrest	2 (6.5%)	2 (6.3%)
• Respiratory pauses with loss of consciousness or gasping for air	6 (19.4%)	7 (21.9%)
• Psychomotor agitation making nursing care impossible and requiring deep sedation	3 (9.7%)	5 (15.6%)
• Sustained bradycardia (HR < 50 bpm with loss of alertness)	2 (6.5%)	2 (6.3%)
• Sustained haemodynamic instability with SBP < 70 mmHg	2 (6.5%)	2 (6.3%)
Presence of minor criteria		
• RR > 35 bpm and above selection RR	10 (32.3%)	18 (56.3%)
• Arterial pH < 7.30 and below selection pH	20 (64.5%)	17 (53.1%)
• PaO2 < 45 mmHg despite oxygen therapy (up to 5 L/min)	1 (3.2%)	1 (3.1%)
• Increase of encephalopathy score	25 (80.6%)	24 (75.0%)

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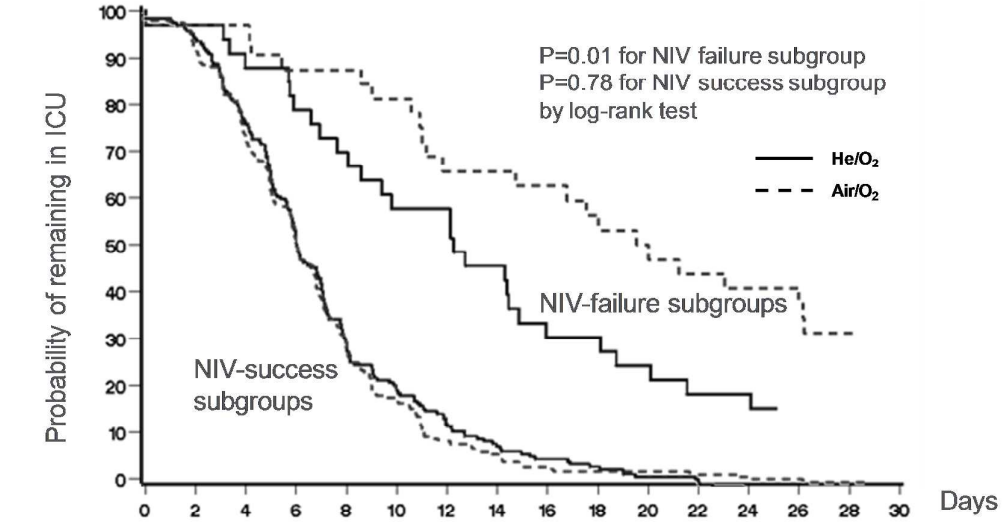
Figure 2e: Probability of remaining in the ICU in the NIV-success (n=380) and NIV-failure ITT subgroups (n=65). He/O_2 full lines, Air/O_2 dashed lines. Log-rank p=0.01 between study gases in NIV-failure subgroup and p=0.78 between study gases in NIV-success subgroup.



No. At Risk			4		8		12		16		20		24			30
He/O_2-success	192	180	146	99	57	39	26	17	12	9	5	3	0			
Air/O_2-success	188	174	137	98	57	36	19	14	9	7	7	6	5	4	3	2
He/O_2-failure	33		30		24		20		11		9		7		5	5
Air/O_2-failure	32		32		29		22		21		17		14		11	8

Table 7e. Most common adverse events. ITT. Adverse events (AEs) reported in more than 3 patients during the treatment period, coded by Preferred Term. Serious adverse events (SAEs) reported in more than 1 patient throughout the study, by MedDRA System Organ Class and Preferred Term.

	He/O_2 (n=225)	**Air/O_2 (n=220)**	**All (n=445)**
Most common AEs of the treatment period			
Bronchospasm	7 (3.1%)	3 (1.4%)	10 (2.2%)
Agitation	1 (0.4%)	5 (2.3%)	6 (1.3%)
Confusional state	4 (1.8%)	0 (0.0%)	4 (0.9%)
Hypokalaemia	3 (1.3%)	1 (0.5%)	4 (0.9%)
Hypertension	3 (1.3%)	1 (0.5%)	4 (0.9%)
Most common SAEs throughout the study			
Respiratory, thoracic and mediastinal disorders	**62 (27.6%)**	**65 (29.5%)**	**127 (28.5%)**
COPD exacerbation	37 (16.4%)	37 (16.8%)	74 (16.6%)
Pneumonia	12 (5.3 %)	21 (9.6%)	33 (7.3%)
Respiratory failure	11 (4.9 %)	8 (3.7 %)	19 (4.3 %)
Pneumothorax	3 (1.3 %)	1 (0.5 %)	4 (0.9 %)
Bronchospasm	2 (0.9 %)	1 (0.5 %)	3 (0.7 %)
Acute pulmonary oedema	1 (0.4 %)	1 (0.5 %)	2 (0.4 %)
Cardiac disorders	**11 (4.9 %)**	**19 (8.6 %)**	**30 (6.7%)**
Cardiac arrest	5 (2.2%)	11 (5.0%)	16 (3.5%)
Left ventricular failure	2 (0.8 %)	4 (1.8 %)	6 (1.4 %)
Infections and infestations	**10 (4.4 %)**	**15 (6.8%)**	**25 (5.6 %)**
Septic shock	7 (3.1 %)	12 (5.5 %)	19 (4.3 %)
General disorders and administration site conditions	**13 (5.8%)**	**6 (2.7%)**	**19 (4.3%)**
Death	9 (4.0%)	4 (1.8%)	13 (2.9%)
Multi-organ failure	3 (1.3 %)	1 (0.5 %)	4 (0.9 %)
Gastrointestinal disorders	**4 (1.8 %)**	**5 (2.3 %)**	**9 (2.0 %)**
Subileus	0 (0.0 %)	3 (1.4 %)	3 (0.7 %)
Nervous system disorders	**2 (0.9 %)**	**6 (2.7 %)**	**8 (1.8 %)**
Hypoxic-ischaemic encephalopathy	2 (0.9 %)	2 (0.9 %)	4 (0.9 %)
Renal and urinary disorders	**2 (0.9 %)**	**3 (1.4 %)**	**5 (1.1 %)**
Acute renal failure	1 (0.4 %)	2 (0.9 %)	3 (0.7 %)
Injury, poisoning and procedural complications	**3 (1.3 %)**	**4 (1.8 %)**	**7 (1.6 %)**
Weaning failure	1 (0.4 %)	2 (0.9 %)	3 (0.7 %)
Neoplasms benign, malignant and unspecified	**3 (1.3 %)**	**2 (0.9 %)**	**5 (1.1 %)**
Malignant neoplasm progression	2 (0.9 %)	0 (0.0 %)	2 (0.4 %)