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Non-invasive Ventilation versus High-Flow Nasal Cannula Oxygen Therapy with apnoeic oxygenation for Pre-Oxygenation before Intubation of Patients with Acute Hypoxemic Respiratory Failure. A randomised multicentre open label trial.

Jean-Pierre Frat, MD¹, Jean-Damien Ricard, PhD², Jean-Pierre Quenot, PhD^{3,4}, Nicolas Pichon, MD⁵, Alexandre Demoule, PhD^{6,7}, Jean-Marie Forel, MD⁸, Jean-Paul Mira, PhD⁹, Rémi Coudroy, MD¹, Guillaume Berquier, MD², Benoit Voisin, MD¹⁰, Gwenhaël Colin, MD¹¹, Bertrand Pons, MD¹², Pierre Eric Danin, MD¹³, Jérôme Devaquet, MD¹⁴, Gwenael Prat, MD¹⁵, Raphaël Clere-Jehl, MD¹⁶, Franck Petitpas, MD¹⁷, Emmanuel Vivier, MD¹⁸, Keyvan Razazi, MD¹⁹, Mai-Anh Nay, MD²⁰, Vincent Souday, MD²¹, Jean Dellamonica, PhD²², Laurent Argaud, PhD²³, Stephan Ehrmann, PhD²⁴, Aude Gibelin, MD²⁵, Christophe Girault, MD²⁶, Pascal Andreu, MD³, Philippe Vignon, PhD^{5,27}, Laurence Dangers, MD⁶, Stéphanie Ragot, PhD²⁸, Arnaud W. Thille, PhD¹, for the FLORALI-2 study group, and REVA network.

Corresponding author:

Jean-Pierre Frat

CHU Poitiers, Service de Médecine Intensive et Réanimation

2, rue de la Milétrie, CS 90577, 86021 POITIERS cedex, France.

Tel: +33 (0) 5 49 44 40 07

Fax: +33 (0) 5 49 44 38 62

e-mail: jean-pierre.frat@chu-poitiers.fr

The authors' affiliations/institutions:

¹ CHU de Poitiers, Médecine Intensive Réanimation, Poitiers, France; INSERM, CIC-1402, équipe ALIVE, Poitiers, France; Université de Poitiers, Faculté de Médecine et de Pharmacie de Poitiers, Poitiers, France.

² Assistance Publique des Hôpitaux de Paris, Hôpital Louis Mourier, Service de Réanimation Médico-Chirurgicale, F-92700, Colombes, France; Université Paris Diderot, UMR IAME 1137, Sorbonne Paris Cité, F-75018, Paris, France ; INSERM, IAME 1137, F-75018, Paris, France.

³ CHU Dijon Bourgogne, service de Médecine Intensive Réanimation, Dijon, France.

⁴ Université Bourgogne Franche-Comté Lipness Team UMR 1231 et INSERM CIC 1432 Epidémiologie Clinique, Dijon, France.

⁵ CHU Dupuytren, Réanimation Polyvalente, F-87042 Limoges, France.

⁶ AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie et Réanimation Médicale du Département R3S, Paris, France.

⁷ Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France.

⁸ Réanimation des Détresses Respiratoires et Infections Sévères, Hôpital Nord – Assistance Publique - Hôpitaux de Marseille, Marseille, France; Aix-Marseille Université, Marseille, France.

⁹ Assistance Publique des Hôpitaux de Paris, Groupe Hospitalier Universitaire de Paris Centre, Hôpital Cochin, Réanimation médicale, Paris, France; Faculté de Médecine, Université Paris Descartes, France.

¹⁰ CHRU de Lille, Centre de Réanimation, Lille, France.

¹¹ Centre Hospitalier Départemental de La Roche sur Yon, Service de Réanimation Polyvalente, La Roche sur Yon, France.

¹² Service de Réanimation, CHU Point-à-Pitre, Pointe-à-Pitre, Guadeloupe, France.

- ¹³ Réanimation Chirurgicale, CHU de Nice, Nice, France; INSERM U1065, team 8, C3M, Nice, France.
- ¹⁴ Hôpital Foch, Réanimation polyvalente, Suresnes, France.
- ¹⁵ CHU de la Cavale Blanche, Service de Réanimation Médicale, Brest, France.
- ¹⁶ Service de réanimation, nouvel hôpital civil, Strasbourg, France ; Université de Strasbourg (UNISTRA), Faculté de Médecine, Hôpitaux universitaires de Strasbourg, France.
- ¹⁷ CHU Poitiers, Réanimation Chirurgicale, Poitiers, France.
- ¹⁸ Centre Hospitalier Saint Joseph-Saint Luc, Service de Réanimation Polyvalente, Lyon, France.
- ¹⁹ Assistance Publique des Hôpitaux de Paris, CHU Henri Mondor, DHU A-TVB, Service de Réanimation Médicale, Créteil, F-94010 France; Université Paris Est Créteil, Faculté de Médecine de Créteil, Groupe de Recherche Clinique CARMAS, Créteil, F-94010, France; INSERM, Unité UMR 955, IMRB, Créteil, F-94010, France.
- ²⁰ Centre Hospitalier Régional d'Orléans, Service de Médecine Intensive réanimation, Orléans, France.
- ²¹ CHU Angers, Service de Réanimation Médicale et Médecine Hyperbare, Angers, France.
- ²² CHU Nice, Service de Médecine Intensive et Réanimation, Nice, France.
- ²³ Hospices Civils de Lyon, Groupement Hospitalier Universitaire Edouard Herriot, Service de Réanimation Médicale, F-69003, Lyon, France.
- ²⁴ CHRU de Tours, Médecine Intensive Réanimation, Tours, France ; Université de Tours, Centre d'Etudes des Pathologies Respiratoires, INSERM U1100, Tours, France.
- ²⁵ Assistance Publique des Hôpitaux de Paris, Hôpital Tenon, Service de Réanimation, pneumologique, Paris, France.

²⁶ Normandie Univ, UNIROUEN, Department of Medical Intensive Care, Charles Nicolle University; Hospital, Rouen, France; EA3830-GRHV, Institute for Research and Innovation in Biomedicine (IRIB), Rouen University, 76000 Rouen, France.

²⁷ Clinical Investigation Centre INSERM 1435, F-87042, Limoges, France.

²⁸ INSERM, CIC-1402, Biostatistics, Poitiers, France; CIC-1402, Poitiers, France; Université de Poitiers, CIC1402, Poitiers, France.

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ABSTRACT

Background: Non-invasive ventilation has never been compared to high-flow oxygen to determine whether non-invasive ventilation reduces the risk of severe hypoxemia during intubation procedure.

Methods: We performed a multicentre, open-label trial in 28 intensive care units in France. Patients undergoing tracheal intubation for acute hypoxemic respiratory failure ($\text{PaO}_2\text{:FiO}_2$ ratio ≤ 300 mm Hg), were randomly assigned to non-invasive ventilation or high-flow oxygen during preoxygenation, with stratification on $\text{PaO}_2\text{:FiO}_2$ level. The primary outcome was the occurrence of severe hypoxemia (pulse oximetry $< 80\%$) during procedure.

Findings: From April 2016 to January 2017, among the 313 patients included in the intention-to-treat analysis, severe hypoxemia occurred in 33 of 142 (23%) patients after preoxygenation with non-invasive ventilation and 47 of 171 (27%) with high-flow oxygen (absolute difference -4.2% , 95% confident interval -13.7 to 5.5 ; $p=0.39$). There was a qualitative interaction between levels of $\text{PaO}_2\text{:FiO}_2$ ratio at baseline and treatment. In the prespecified stratum of the 242 patients with moderate-to-severe hypoxemia ($\text{PaO}_2\text{:FiO}_2 \leq 200$ mm Hg), severe hypoxemia occurred in 28 of 117 (24%) patients after preoxygenation with non-invasive ventilation and 44 of 125 (35%) with high-flow oxygen: adjusted odds ratio 0.56 (95% CI, 0.32 - 0.99 , $p=0.0459$). In the 71 patients with mild hypoxemia ($\text{PaO}_2\text{:FiO}_2 > 200$ mm Hg), there was no difference in primary outcome.

Interpretation: In patients with acute hypoxemic respiratory failure, preoxygenation with non-invasive ventilation or high-flow oxygen therapy did not change the risk of severe hypoxemia. This risk seems to be decreased with non-invasive ventilation for patients with moderate-to-severe hypoxemia.

Key words: preoxygenation, non-invasive ventilation, high-flow oxygen, respiratory failure.

Funding: Financial support was provided by the “Programme Hospitalier de Recherche Clinique National” 2015 of the French Ministry of Health.

The firm “Fisher & Paykel HealthCare” provided the equipment for some of the participating centers.

Research in context panel

Evidence before this body

We searched PubMed from Jan 1, 2000 to Oct 1, 2018 using the following search terms: “preoxygenation” or “pre-oxygenation” and “apneic oxygenation” and “non-invasive ventilation”. The literature shows one small randomised control study reporting better efficacy of non-invasive ventilation in preventing severe hypoxemia before intubation as compared to standard oxygen using valve-bag mask in patients with acute hypoxemic respiratory failure. Another study showed a lower incidence of severe hypoxemia with high-flow oxygen therapy as compared to standard oxygen in a prospective before-after study, however these results were not confirmed in the different randomized controlled trials carried out to date. It therefore raises the question whether NIV as compared to high-flow oxygen therapy could better prevent severe hypoxemia during the intubation procedure of patient with hypoxemic respiratory failure.

Added value of this study:

This multicentre randomised controlled trial shows that preoxygenation with non-invasive ventilation or high-flow oxygen therapy carried out in patient ongoing intubation for acute hypoxemic respiratory failure did not change the risk of oxygen severe desaturation or other complications. However, episodes of severe oxygen desaturation were less frequent after preoxygenation with non-invasive ventilation in the prespecified stratum of the subgroup of patients with severe-moderate hypoxemia whatever the previous treatment carried out before randomization. Additionally, the lowest pulse oximetry was significantly higher after preoxygenation with non-invasive ventilation than high-flow oxygen.

Implications of all the available evidence:

The findings of the FLORALI-2 trial lead to carry out non-invasive ventilation during preoxygenation before intubation of patients with severe hypoxemic respiratory failure. This

subgroup of patients represents more than three quarter of patients with acute hypoxemic respiratory failure. In view of these results and previous studies, preoxygenation with valve-bag facemask should be replaced by high-flow nasal cannula oxygen therapy or non-invasive ventilation in ICU before intubation of patients with acute mild hypoxemic respiratory failure. However, further study should be conducted to investigate whether non-invasive ventilation might be carried out in all patients whatever their level of hypoxemia in a larger population of patients with acute hypoxemic respiratory failure during preoxygenation before intubation.

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INTRODUCTION

Tracheal intubation is one of the most commonly performed procedures in intensive care units (ICUs).¹ Unlike the operating room, intubation procedure in ICU carries a high risk of life-threatening complications including severe hypoxemia, neurological or cardiac ischemia, and cardiovascular collapse.^{2, 3} Severe hypoxemia occurs in 20-25% of cases especially in hypoxemic patients intubated for acute respiratory failure.²⁻⁴ Cardiac arrest is the ultimate catastrophic complication, which can occur in 2-3% of intubation procedure in ICU, and is strongly related to hypoxemia or absence of preoxygenation before intubation.^{5, 6} Consequently, optimization of pre-oxygenation may help to secure the procedure by mitigating the risks of severe hypoxemia and subsequent complications.

Non-invasive ventilation and high-flow nasal cannula oxygen therapy (high-flow oxygen) are two oxygenation devices largely used in ICU that provide higher fraction of inspired oxygen (FiO₂) than standard oxygen.⁷⁻¹⁰ High-flow oxygen enables delivery of continuous high gas flow via nasal prongs resulting in higher FiO₂ than with standard oxygen.⁷ Another theoretical advantage of high-flow oxygen may consist in maintaining oxygenation during the apnoeic phase of intubation after anaesthetic induction, thereby avoiding hypoxemia whereas non-invasive ventilation is removed at this phase. Only one randomised controlled study including a small sample of patients with acute hypoxemic respiratory failure has shown better efficacy of non-invasive ventilation in preventing severe hypoxemia as compared to standard oxygen using valve-bag mask.¹¹ Another study showed a higher rate of severe hypoxemia with standard oxygen than with non-invasive ventilation in the subgroup of patients previously treated with non-invasive ventilation.¹² High-flow oxygen has also shown a lower incidence of severe hypoxemia during intubation procedure as compared to standard oxygen in a

prospective before-after study.¹³ However, these encouraging results were not confirmed in the different randomised controlled trials carried out to date.¹⁴⁻¹⁶

We conducted a prospective, multicentre, randomised, controlled trial involving patients admitted to the ICU with acute hypoxemic respiratory failure and undergoing tracheal intubation with the hypothesis that non-invasive ventilation could be associated with a lower rate of severe hypoxemia during the procedure as compared to high-flow oxygen therapy.

METHODS

Trial Design and Oversight

The high-Flow oxygen for pre-Oxygenation as Respiratory support during Acute Lung Injury before Intubation (FLORALI-2) trial was a non-blinded, multicentre, open-label, 2 parallel-group randomised, controlled clinical trial (RCT). In the trial, patients from 28 ICUs in France were randomly assigned (1:1) to receive either non-invasive ventilation or high-flow oxygen therapy during pre-oxygenation.

The study protocol was approved for all centres by the ethics committee at Poitiers University Hospital (Ethics Committee Ouest III, Poitiers, France, registration number 2015-A00530-49). According to the French law and decision of the ethics committee, no safety committee was required, because the interventions used in the study were strategies of preoxygenation that are usually carried out in clinical practice. Inclusions were performed after having obtained informed consent from all patients or next of kin. The trial was overseen by a steering committee that presented information regarding the progression and monitoring of the study at Réseau Européen de Recherche en Ventilation Artificielle (REVA) Network meetings to all the investigators and/or research assistants of the participating centres every 4 months. Moreover, the role of the steering committee included making decisions, endorsing actions of the clinical research team and working with the public funder (University hospital

of Poitiers). Members of the steering committee were not independent and were also members of the scientist committee, who designed the study. Members checked all relevant publications on the field of the study to ensure consistency in continuing the study. However, they had no access to the data collected or database until it was locked after the monitoring of centres. Research assistants regularly monitored all centres on-site to check adherence to the protocol and accuracy of the data recorded in accordance with the Good Clinical Practice Guidelines. An investigator at each centre was responsible for enrolling patients in the study, ensuring adherence to the protocol and completing the electronic case-report form.

Patients

Consecutive patients older than 18 years admitted to the ICU and requiring intubation could be enrolled if they had acute hypoxemic respiratory failure according to the following criteria: a respiratory rate above 25 breaths/min or signs of respiratory distress, and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ($\text{PaO}_2:\text{FiO}_2$ ratio) equal to or below 300 mm Hg regardless of oxygenation strategy. For the calculation of $\text{PaO}_2:\text{FiO}_2$ ratio, FiO_2 was measured under non-invasive-ventilation or high-flow oxygen and estimated under standard oxygen as follows: $\text{FiO}_2 = 0.21 + \text{oxygen flow rate} \times 0.03$.¹⁰

The main exclusion criteria were as follows: intubation for cardiac arrest, altered consciousness defined by a Glasgow coma score <8 points, other contraindications to non-invasive-ventilation (recent laryngeal, oesophageal or gastric surgery, and significant facial fractures), pulse oximetry not available, pregnant or breast-feeding women, and refusal to participate.

Randomization and Allocation Concealment

Randomization was computer-performed in permuted blocks of four (unknown to investigators), with stratification according to centre and level of the $\text{PaO}_2:\text{FiO}_2$ ratio (equal to or below 200 and above 200 mm Hg). Within one hour after the validation of inclusion

criteria, patients were randomly assigned in a 1:1 ratio, with the use of a centralised Web-based management system (G-ERDC, Clinfile, France), to one of the two following strategies: high-flow oxygen therapy or non-invasive ventilation.

Blinding

Although individual patient assignments could not be masked, the coordinating centre and all the investigators remained unaware of the study-group outcomes until the data were locked in October 2017. An adjudication committee unaware of the study groups reviewed all the data of pulse oximetry recorded and stored so as to analyse the events occurring during the intubation procedure, after an independent biostatistician, who was unaware of the study group outcomes collected data of patients from the recordings, with extraction of pulse oximetry curves and values. All analyses were performed by the study statistician in accordance with both the International Conference on Harmonization and Good Clinical Practice Guidelines. The complete methodology of the study has been previously published.¹⁷

Interventions

Preoxygenation was carried out in a semi-recumbent position at 30° for 3–5 min with the technique assigned by randomization whatever the previous technique used for oxygenation.

In the non-invasive ventilation group, preoxygenation was delivered with a face mask connected to an ICU ventilator. Pressure-support ventilation was adjusted to obtain an expired tidal volume between 6 and 8 mL/kg of predicted body weight with a positive end-expiratory pressure (PEEP) level of 5 cm H₂O and a FiO₂ of 1.0. Consequently, non-invasive ventilation provides oxygenation and ventilation during preoxygenation, between induction and laryngoscopy, but neither oxygenation nor oxygenation during laryngoscopy.

In the high-flow oxygen group, preoxygenation was delivered by applying oxygen continuously via bi-nasal prongs, with a gas flow of 60 L/min through a heated humidifier

(MR 850, Fisher & Paykel, Auckland, New Zealand) and a FiO_2 of 1.0. Clinicians were instructed to perform a jaw thrust so as to maintain patent upper airway and to maintain the high-flow oxygen therapy during all the procedure of laryngoscopy until the endotracheal tube was placed into the trachea. Consequently, high-flow oxygen provides oxygenation but with little ventilation during preoxygenation, between induction and laryngoscopy, and also during laryngoscopy.

Bundle management including the following measures was proposed to all the participating centres for the intubation procedure as previously described⁴: the presence of two operators, systematic fluid loading before intubation (isotonic saline or balanced crystalloids at the discretion of the physician in charge of the patient) in absence of cardiogenic pulmonary oedema and rapid-sequence induction using etomidate (0.2–0.3 mg/kg) or ketamine (1.5–3 mg/kg) combined with rocuronium (0.6–1 mg/kg) or succinylcholine (1 mg/kg). In case of unsuccessful intubation, the following algorithm according to a given centre's procedure was proposed: an introducer first (intubating stylet or Eschmann introducer), then videolaryngoscopy, an intubation laryngeal mask airway, and finally fiberscopy and rescue percutaneous or surgical tracheostomy. After endotracheal intubation, patients were mechanically ventilated with a tidal volume of 6 ml/kg of predicted body weight, a respiratory rate of 25–30 breaths/min, a PEEP of 5 cm H_2O and a FiO_2 set to maintain a pulse oximetry above 90%.

Study Outcomes

The primary outcome was the occurrence of an episode of severe hypoxemia defined by a decrease in pulse oximetry below 80% for at least 5 seconds between the beginning of rapid-sequence induction (end of preoxygenation) and 5 min after confirmation of the tracheal intubation by capnography. To ensure that all centres have equivalent monitoring of pulse oximetry, a dedicated portable pulse oximetry monitor (Covidien, Nelcor DS 100A) and

single-patient-use digital sensors (Covidien, Max-A-I) were provided to all the participating centres. All values of pulse oximetry were recorded with a 1 Hz frequency (one value of pulse oximetry by second) during the procedure and stored for subsequent analysis.

Secondary outcome variables were collected at the bedside in a separate form by physicians, residents or nurses and included the value of pulse oximetry at the end of preoxygenation and the lowest value during intubation procedure. Other prespecified outcomes included feasibility of preoxygenation evaluated by a 4-points scale (easy, quite easy, quite difficult, difficult), Cormack grade,¹⁸ intubation difficulty scale,¹⁹ difficulty for intubation (>2 laryngoscopic attempts to place the endotracheal tube into the trachea or as lasting more than 10 minutes using conventional laryngoscopy, MACOCHA score),^{20, 21} immediate complications (arterial hypotension, sustained cardiac arrhythmia, bradycardia, cardiac arrest, death, oesophageal intubation, regurgitation, gastric distension, dental injury and new infiltrate on chest radiograph,) and late complications (occurrence of ventilator-associated pneumonia, worsening of SOFA score²² from day 1 to day 7, duration of mechanical ventilation, ICU length of stay and mortality at day 28).

Sample Size

Assuming a rate of severe hypoxemia episodes of 25% in patients having preoxygenation with high-flow oxygen,^{15, 16} we calculated that enrolment of 320 patients would provide the study with 95% power to show an absolute difference of 15% percentage points in the primary outcome between the high-flow oxygen therapy and non-invasive-ventilation group^{4, 11} at a two-sided alpha level of 0.05.

Statistical Analysis

Analyses were performed in the intention-to-treat population and in pre-specified subgroups determined by the stratification variable, moderate-to-severe hypoxemic patients with a PaO₂:FiO₂ ratio equal to or below 200 mm Hg vs. mild hypoxemic patients with PaO₂:FiO₂

ratio above 200 mm Hg. Baseline characteristics in each study group were analysed as frequencies and percentages for categorical variables and as means and SDs for continuous variables, as appropriate.

The primary analysis compared the incidence of severe hypoxemia between the non-invasive ventilation group and the high-flow oxygen group using an unadjusted Chi-square test. Heterogeneity of treatment effects across these pre-specified subgroups was examined by testing for treatment-covariate interaction with the logistic regression model. Adjustment on baseline level oxygenation was performed using logistic regression.

The secondary analyses compared secondary outcomes using an unadjusted Chi-square test for categorical variables and the Student's t-test or the Mann-Whitney test for continuous variables.

A two-tailed P value of less than 0.05 was considered to indicate statistical significance. No allowance for multiplicity has been performed, all secondary outcomes should be considered exploratory.

We used SAS software, version 9.4 (SAS Institute), for all the analyses.

Role of the funding source

Financial support was provided by the following organizations, which had no other involvement in the study: the French Ministry of Health supported the study through the grant "Projet Hospitalier de Recherche Clinique National" grant of year 2015; the "Fisher & Paykel Health Care" firm provided the equipment for all the participating centers.

The corresponding author had full access to all the data and the final responsibility to submit for publication. The biostatistician (SR) had access to the raw data.

RESULTS

Recruitment

From April 2016 to January 2017, a total of 2079 patients were intubated in the 28 participating ICUs, and 322 underwent randomization. After the secondary exclusion of five patients having no recorded data, two patients having withdrawn consent or being under legal protection, one not intubated and one having cardiac arrest, 313 patients were included in the analysis (**Figure 1**). Among them, 142 patients were assigned to non-invasive ventilation and 171 to high-flow oxygen therapy. The median interval between ICU admission and randomization was 1 day (interquartile range (IQR), 0 to 2).

Baseline Data

The characteristics of patients at enrolment did not differ between the two groups (**Table 1** and **Table S1 in appendix**). The mean settings were as follows: in the non-invasive ventilation group, a pressure support level of 9 ± 4 cm H₂O, a PEEP of 5 ± 0.5 cm H₂O, and a FiO₂ of 0.99 ± 0.06 , resulting in a tidal volume of 8.3 ± 2.6 ml per kilogram of predicted body weight; in the high-flow oxygen group, a gas flow of 58 ± 9 litres per minute with a FiO₂ of 0.99 ± 0.08 . The duration of preoxygenation lasted 5 ± 2 minutes with non-invasive ventilation and 5 ± 4 with high-flow oxygen ($p=0.45$).

Primary Outcome

In the overall study population, the proportion of patients with severe hypoxemia was 23% (33 of 142 patients) after preoxygenation by non-invasive ventilation and 27% (47 of 171) after high-flow oxygen (absolute difference -4.2%, 95% confident interval (CI) -13.7 to 5.5; $p=0.39$) (**Table 2**). Significant interaction was found between PaO₂:FiO₂ level at enrollment and the treatment group with respect to status regarding the primary outcome (**Figure S2 in appendix**). Consequently, results were split in two subgroups:

patients with moderate-to-severe hypoxemia ($\text{PaO}_2\text{:FiO}_2$ equal to or below 200), and patients with mild hypoxemia ($\text{PaO}_2\text{:FiO}_2$ ratio above 200 mm Hg).

In the subgroup of patients with moderate-to-severe hypoxemia, the severe hypoxemia rate occurred in 28 (24%) of 117 patients in the non-invasive ventilation group and 44 (35%) of 125 patients in the high-flow oxygen group (absolute difference estimate -11.3% , 95% CI -22.3 to 0.3 , $p=0.055$) (**Table 3**). The risk of severe hypoxemia was significantly lower with non-invasive ventilation than with high-flow oxygen after adjustment for PaO_2 at randomization, adjusted odds ratio 0.56 (95% CI, 0.32 - 0.99 , $p=0.0459$) (**Table 3**).

In the subgroup of patients with mild hypoxemia, there was no difference in severe hypoxemia rates, 5 (20%) of 25 patients and 3 (7%) of 46 in non-invasive ventilation and high-flow oxygen therapy group, respectively (absolute difference estimate 13.4% , 95% CI -2.2 to 33.1 , $p=0.12$) (**Table 3**).

Secondary Outcomes

In the overall study population, pulse oximetry values, duration of laryngoscopy or procedure of tracheal intubation were not different between the two strategies of preoxygenation (**Table 2**). There was also significant interaction between $\text{PaO}_2\text{:FiO}_2$ level at enrollment and the treatment group with respect to status regarding the lowest pulse oximetry during the intubation procedure (Figure S2 in appendix).

In the subgroup of patients with moderate-to-severe hypoxemia, the lowest pulse oximetry during intubation procedure was significantly higher in the non-invasive ventilation group as compared with the high-flow oxygen group, $86\pm 12\%$ versus $81\pm 17\%$ ($p=0.02$) (**Table 3**, **Figure 2** and **Figure S1 in appendix**). Similarly, the pulse oximetry at the end of preoxygenation was higher in the non-invasive ventilation group as compared with the high-flow oxygen group.

In the subgroup of patients with mild hypoxemia, there was no difference in pulse oximetry at the end of preoxygenation and during intubation procedure ($p=0.31$) (**Table 3, Figure 2 and Figure S1 in appendix**).

Feasibility, complications and clinical outcomes

Preoxygenation during intubation procedure was perceived by practitioners as “easy” or “quite easy” in 94% of cases (134 of 142 patients) with non-invasive ventilation and 94% of cases (161 of 171 patients) with high-flow oxygen (**Table S2 in appendix**).

Preoxygenation was aborted in 3 patients during non-invasive ventilation and in 6 during high-flow oxygen therapy, mainly due to severe hypoxemia (5 of 9 patients). Rates of immediate and late complications did not differ between the two treatment groups (**Table 2**). Cumulative probability of survival was not different between both strategies of preoxygenation whatever the subgroup of patients (**Table 2 and Figure S3 in appendix**).

DISCUSSION

In this multicentre, randomised, open-label trial including patients with acute hypoxemic respiratory failure ($\text{PaO}_2:\text{FiO}_2$ ratio of 300 mm Hg or less), preoxygenation with non-invasive ventilation as compared with high-flow oxygen therapy did not change the risk of severe hypoxemia during intubation procedure or the occurrence of late complications. Baseline $\text{PaO}_2:\text{FiO}_2$ ratio appeared to modify the effect of preoxygenation strategies on the risk of severe hypoxemia, with secondary analyses suggesting a possible benefit of non-invasive ventilation among patients with moderate-to-severe hypoxemia.

When planning the study, we assumed a reduction rate of severe hypoxemia from the usual 25% to 10%. This reduction could seem optimistic, however most of the studies reported a rate of severe hypoxemia of 25%, with high-flow oxygen or standard oxygen

preoxygenation.^{3, 14-16} In the non-invasive ventilation group, we based our estimation of severe hypoxemia on two previous studies reporting a rate of 10% or less.^{4, 11}

Our results showed a rather high rate around 25% in both groups. Accurate off-line analysis of pulse oximetry recordings during the whole intubation procedure period using a dedicated monitor may have identified otherwise unrecognised events and subsequently increased the rates of severe hypoxemia. Intubation procedure is sometimes urgent, difficult and confusing and it may be difficult to detect all episodes of severe hypoxemia, which could lead to an underestimation of events.

Otherwise, it seems there was an imbalance in stratification factors especially in the subgroup of patients with mild hypoxemia. In fact, the observed imbalance was 21 patients in this stratum. This can be explained by the stratification according to the PaO₂:FiO₂ ratio level and to centres with randomisation performed in permuted blocks of four. The maximum theoretical imbalance between the two groups of treatment for a given stratum in a given centre was two patients. As 21 among the 28 participating centres have included patients in this stratum, the final imbalance could have reached up to 42 patients,

In order to explore effects of pre-oxygenation strategies in hypoxemic patients, we planned subgroups analysis according to the severity of hypoxemia based on the classification of the acute respiratory distress syndrome (moderate-to-severe versus mild).²³ These subgroups included strata determined by PaO₂:FiO₂ ratio level (equal to or below 200 and above 200 mm Hg) at randomization regardless the oxygen device applied before pre-oxygenation. Our results showed qualitative effect of treatment across these two predefined subgroups for severe hypoxemia supported by a significant test of interaction.²⁴ Finally, the impact of non-invasive ventilation on severe hypoxemia was different according to the prespecified subgroup, and appeared to be beneficial during pre-oxygenation only in patients with moderate-to-severe hypoxemia.

Previous studies have never compared effects of non-invasive ventilation with high-flow oxygen. In three randomized controlled studies, high-flow oxygen usually set with a gas flow of 50L/min and a FiO₂ of 100% was compared to standard oxygen preoxygenation, but high-flow oxygen had never been found to be superior to standard oxygen preoxygenation.¹⁴⁻¹⁶ One previous pilot study including 53 patients found that non-invasive ventilation was superior to valve-bag mask during preoxygenation in avoiding risk of severe hypoxemia and obtaining higher pulse oximetry.^{11, 12} However, none of these studies evaluated effects of preoxygenation strategies according to the level of oxygenation in patients with respiratory failure. A recent study showed that non-invasive ventilation during preoxygenation was more efficient than bag valve-mask oxygen to prevent severe hypoxemia in a subgroup of patients previously treated with non-invasive ventilation.¹² One explanation might be that these patients were more severe than those treated with standard oxygen. In our study, non-invasive ventilation was also beneficial for preoxygenation of the most severe patients, although the oxygen device applied prior to inclusion, *i.e.* non-invasive ventilation, standard oxygen or high-flow oxygen, was not independently associated with severe hypoxemia.

The significantly higher pulse oximetry at the end of preoxygenation with non-invasive ventilation may explain its potential positive effect during preoxygenation among moderate-to-severe hypoxemic patients. Physiologic effects of non-invasive ventilation include the ability to rapidly improve¹¹ oxygenation similarly to invasive ventilation,²⁵ through delivery of high levels of FiO₂ and intrathoracic positive pressures favouring the increase of lung volumes or alveolar recruitment.⁹ High-flow oxygen may have similarly rapid effect, *i.e.* positive end-expiratory pressure effect with an increased end-expiratory lung volume,²⁶ but with a lower magnitude than non-invasive ventilation.^{8, 10} In fact, high-flow oxygen may generate a positive end-expiratory ranging from 1 to 3cm of water in patient with respiratory failure, a level lower than that obtained with non-invasive ventilation.²⁷ Consequently, the

effect of apnoeic oxygenation during laryngoscopy under high-flow oxygen does not seem as efficient as high positive pressures delivered by non-invasive ventilation as a mean of preventing hypoxemia.

There was no impact on mortality of pre-oxygenation strategies whatever the subgroup of patients. In fact, the intubation procedure is at risk of mortality during the procedure or immediately after starting the mechanical ventilation, especially in severe hypoxemic patients. However, it seems that there is no specific risk of delayed mortality within the following days. Our trial had several strengths that suggest that the results are applicable for most of patients with acute hypoxemic respiratory failure requiring intubation in ICUs. These strengths included the multicentre design and sealed randomization to the assigned technique of preoxygenation, subgroups analysis enabling to detect differences across strata, a well-defined protocol that included the adjudication of downloaded pulse oximetry recordings of each patient with the same dedicated portable pulse oximetry monitor among centres, complete follow-up at 28 days, and an intention to treat analysis.

Limitations of our study could be first, to have not considered a strategy of preoxygenation with valve-bag facemask in the control group. As high-flow oxygen therapy has showed efficacy in the management of patients with acute respiratory failure,¹⁰ and at least as efficient as valve-bag facemask for pre-oxygenation,^{13, 16} consequently most of investigators were concerned about switching to a preoxygenation with valve-bag facemask, which could be potentially less effective to improve oxygenation.¹³ Second, a high proportion of patients who were intubated in ICUs during the study period were not included that may limit generalization of findings. Many of the patients excluded from the study were not hypoxemic, underwent urgent intubation or had cardiac arrest or coma. However, these two last situations are not frequent reasons of intubation during acute hypoxemic respiratory failure and represent contraindications to non-invasive ventilation.¹⁰ Third, our primary outcome was not

a patient-important outcome,²⁸ however most of previous randomised, controlled studies^{11, 12, 14-16, 29} assessed hypoxemia as primary outcome, which should be considered as a surrogate endpoint³⁰ for hypoxia-driven cardiac arrests. Last, because treatments allocation could not be blinded, pulse oximetry curves were recorded and downloaded to be evaluated by blinded adjudicators in order analysing the events occurring during intubation procedure.

In conclusion, preoxygenation with non-invasive ventilation or high-flow oxygen therapy during intubation procedure did not change the risk of severe hypoxemia and other immediate or late complications. However, non-invasive ventilation may prevent severe hypoxemia among patients with severe-moderate hypoxemia as compared with high-flow oxygen. This finding calls for confirmation in future research.

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Author contribution:

JPF: investigator of the study, study design, member of the steering committee, data acquisition and collection, data analysis and interpretation, drafting the manuscript.

JDR, AWT: study design, data acquisition and collection, data analysis and interpretation, draft of the manuscript, critical revisions of the manuscript for important intellectual content.

JPQ, NP, AD, JMF, JPM, RC, GB, BV, GC, BP, PED, JD, GP, RCJ, FP, EV, KR, MAN, VS, JD, LA, SE, AG, CG, PA, PV, and LD: data acquisition and collection, critical revisions of the manuscript for important intellectual content.

SR: data analysis and data interpretation.

Conflict of interest statement:

Dr. Frat reports grants from the French Ministry of Health; grants, personal fees and non-financial support from Fisher & Paykel HeathCare, during the conduct of the study; personal fees and non-financial support from SOS oxygene, outside the submitted work.

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Dr. Thille reports travel and accommodation expense coverage to attend scientific meetings from Covidien, General Electric Healthcare, Fisher&Paykel, Maquet - Getinge, and reports no income or personal fees from no company

The other authors declared no conflicts of interest.

Data sharing:

Data collected for the study are not available.

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FIGURE LEGENDS

Figure 1: Flow of participants through the high-flow oxygen for pre-oxygenation as respiratory support during acute lung injury before intubation (florali-2) randomised clinical trial. **Figure 2:** Variations in mean values of minimal pulse oximetry from baseline to the end of the intubation procedure, **(A)** in the overall population, **(B)** in patients with moderate to severe hypoxemia ($\text{PaO}_2:\text{FiO}_2 \leq 200$ mm Hg) and **(C)** in patients with mild hypoxemia ($\text{PaO}_2:\text{FiO}_2 > 200$ mm Hg), in the non-invasive ventilation group (red line) and high-flow nasal cannula oxygen therapy group (blue line). Points and squares represent mean values with the 95% confident interval. At baseline (defined as values obtained at time of randomization), pulse oximetry values were similar. Values of pulse oximetry at the end of preoxygenation and lowest pulse oximetry values during intubation procedure were higher after preoxygenation with non-invasive ventilation than with high-flow oxygen ($p=0.02$) in patients with moderate-to-severe hypoxemia. **Figure S1:**

(A) Rates of severe hypoxemia during intubation procedure after preoxygenation with non-invasive ventilation (NIV, red bar) and high-flow oxygen therapy (HFOT, blue bar), in the overall population and subgroups of strata.

(B) Lowest pulse oximetry values during intubation procedure after preoxygenation with non-invasive ventilation (NIV, red points) and high-flow nasal cannula oxygen therapy (HFOT, blue points) in the overall population and subgroups of strata.

Figure S2:

(A) Forest plot showing primary outcome (severe oxygen desaturation) broken down by the $\text{PaO}_2:\text{FiO}_2$ stratum, the vertical line set at 15% corresponds to the expected difference between the two treatments. The value 15% is within the 95% confidence interval for the stratum $\text{PaO}_2:\text{FiO}_2 \leq 200$.

(B) Restricted cubic spline regression between $\text{PaO}_2:\text{FiO}_2$ ratio at baseline and lowest SpO_2 value for noninvasive ventilation (red line) and high-flow oxygen (blue line) showing the qualitative interaction between the level of $\text{PaO}_2:\text{FiO}_2$ baseline and treatment ($p=0.047$). The cut point of $\text{PaO}_2:\text{FiO}_2$ level effect is nearly 200 mmHg at which the sign is swapped for the treatment.

Figure S3: Kaplan-Meier Plot of the Probability of Survival from Randomization to Day 28, (A) in the intention-to-treat population, (B) subgroups of patients with PaO₂/FiO₂ ratio ≤200 mm Hg and (C) PaO₂/FiO₂ ratio >200 mm Hg, according to study groups. HFOT denotes high flow nasal cannula oxygen therapy, NIV noninvasive ventilation.

3776 Patients intubated during the study period, April 2016-
January 2017

1697 Were intubated prior to ICU admission

2079 Patients intubated in ICUs

1334 Were excluded because:

243 Had a PaO₂:FiO₂ ratio >300 mm Hg

74 Had a respiratory rate <25 breaths/min
or absence signs of respiratory distress

465 Had Glasgow Coma scale <8

169 Were in cardiac arrest

37 Had difficult intubation criteria

202 Had an urgent intubation

61 Had contraindications to noninvasive
ventilation

2 Had allergy or contraindication to
anesthetic drugs

81 Had administrative reasons

745 Eligible for inclusion

423 Were excluded

4 For pulse oxymetry dysfunction

88 Declined to participate

331 Had logistical reasons

322 Randomized

147 Assigned to Noninvasive-
ventilation group
1 Not intubated
1 Was under law protection
3 Had no recorded data

142 Included in the intention-to-treat
analysis and in the 28-day follow up

175 Assigned to High-Flow Oxygen
group
1 Withdrew consent
1 Did not receive treatment
2 Had no recorded data

171 Included in the intention-to-treat
analysis and in the 28-day follow up

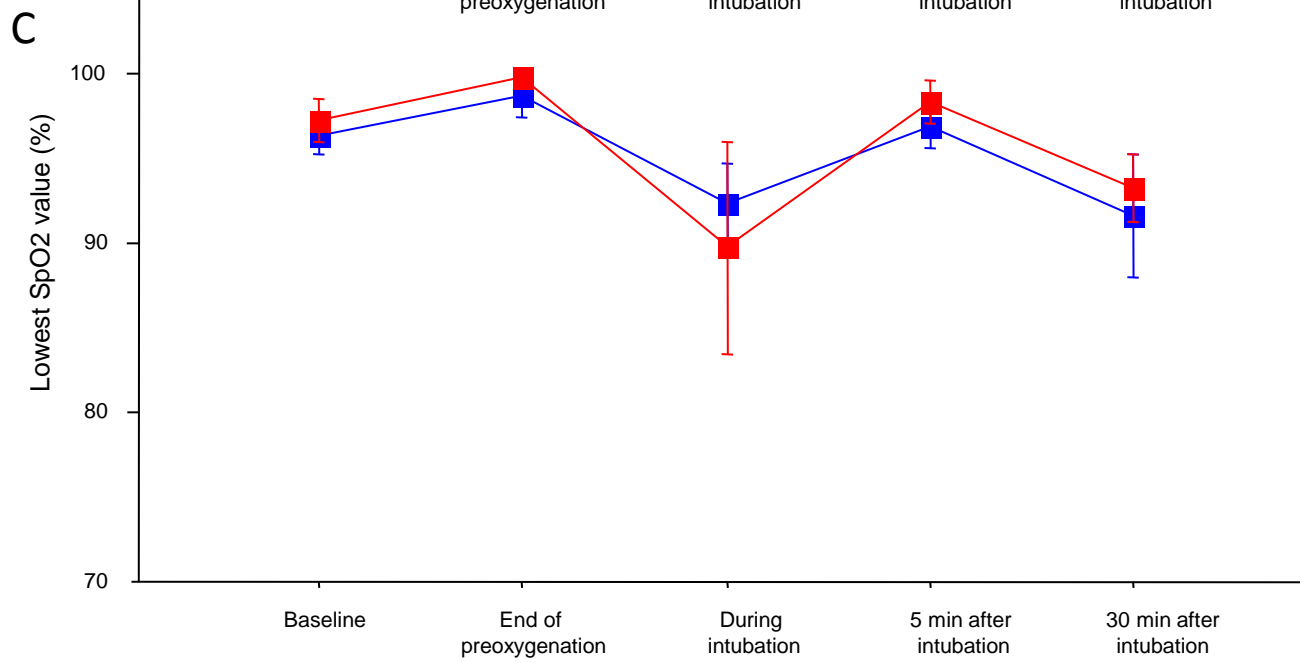
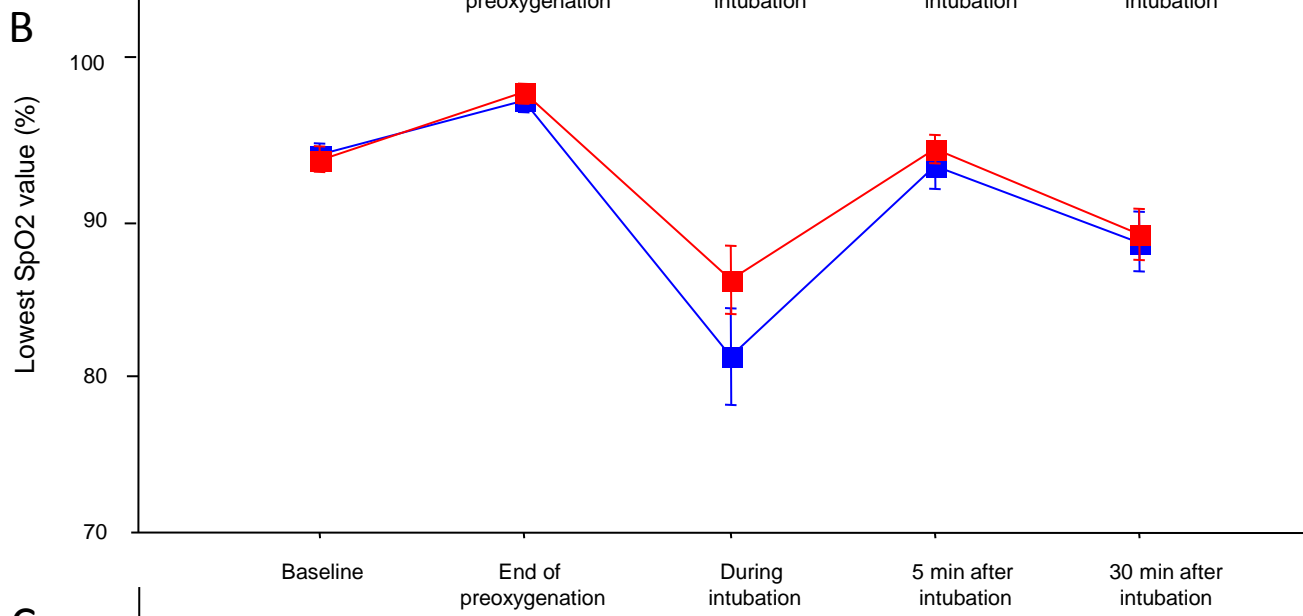
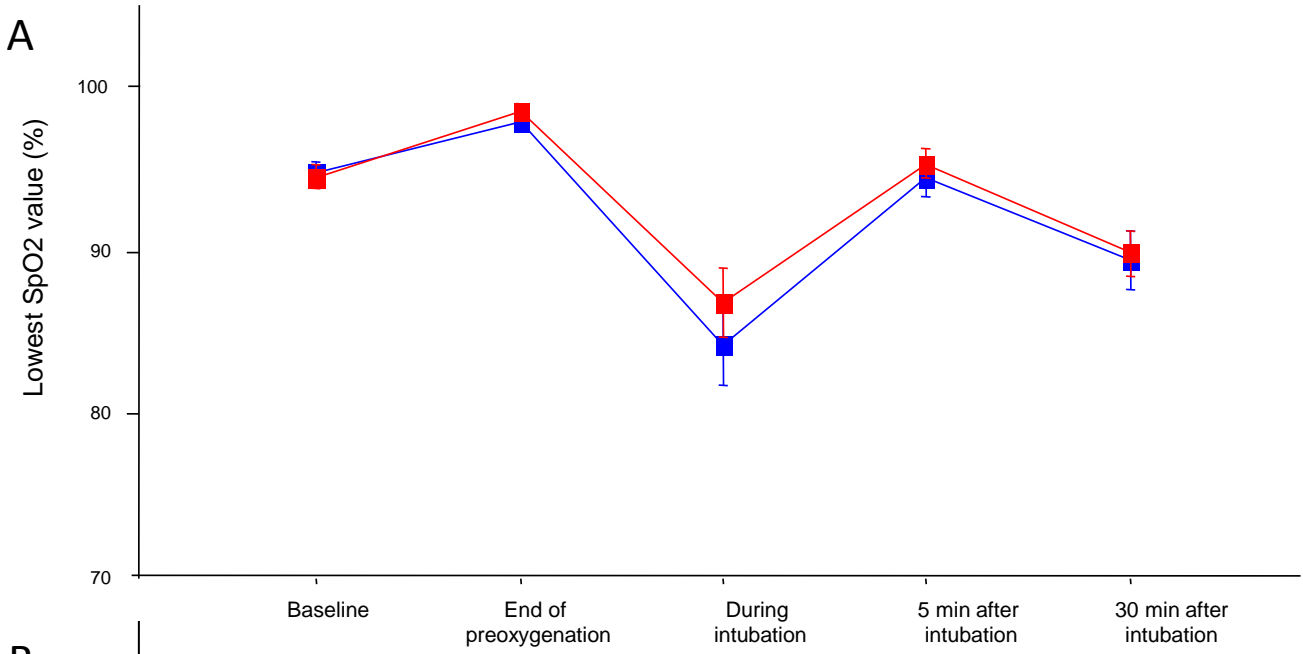


Table 1: Baseline Characteristics of the Intention-to-Treat Population according to Study Group

	NIV (n=142)	HFOT (n=171)	p value
Age, year	64±13	64±14	0.74
Male sex, n (%)	101 (71)	111 (65)	0.24
Body-mass index, ^a kg/m ²	27±7	27±6	0.90
SAPS II ^b , point	52±20	51±19	0.85
SOFA at inclusion, ^c point	5±3	6±3	0.31
Underlying chronic lung disease, n (%)	52 (37)	53 (31)	0.23
Past upper airway tract cancer, n (%)	4 (3)	4 (2)	0.99
Reason for ICU admission, n (%)			0.31
Respiratory primary failure			
Respiratory infection	50 (35)	60 (35)	
COPD exacerbation	8 (6)	8 (5)	
Extra-pulmonary ARDS	4 (3)	2 (1)	
Pulmonary atelectasis	2 (1)	2 (1)	
Other	17 (12)	16 (9)	
Non-respiratory primary failure			
Shock	24 (17)	42 (25)	
Cardiogenic pulmonary oedema	10 (7)	7 (4)	
Neurologic	7 (5)	6 (4)	
Other	13 (9)	23 (13)	
Post-operative	7 (5)	5 (3)	
Oxygen device the last hour before inclusion, n (%)			0.90
Standard oxygen	63 (44)	73 (43)	
HFOT	48 (34)	57 (33)	
NIV	31 (22)	41 (24)	
Vasopressor support at inclusion, n (%)	27 (19)	35 (20)	0.75
Bilateral pulmonary infiltrates, n (%)	88 (73)	106 (73)	0.98
Respiratory rate, breaths/min	30±8	31±8	0.35
PaO ₂ :FiO ₂ ratio, mm Hg	142±65	148±70	0.40
Stratification sub-groups, n of patients/total, n (%)			0.06
PaO ₂ :FiO ₂ ratio > 200 mm Hg	25 (18)	46 (27)	
PaO ₂ :FiO ₂ ratio ≤ 200 mm Hg	117 (82)	125 (73)	
MACOCHA score, ^d n (%)			0.83
<3	119 (84)	144 (85)	
≥3	23 (16)	26 (15)	
Cormack III or IV, n of patient/total, ^e n (%)	13 (9)	16 (9)	0.95
Intubation Difficulty Scale, ^f n (%)			0.53
≤5	121 (87)	151 (89)	
>5	18 (13)	18 (11)	

The data are means ± SD or absolute numbers (%). Reason for ICU admission was compared in 3 classes with chi² test: respiratory primary failure, non-respiratory primary failure, post-operative.

Abbreviations: SD, standard deviation; NIV, non-invasive ventilation; HFOT, high flow nasal cannula oxygen therapy; COPD, chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome.

^a The body-mass index is the weight in kilograms divided by the square of the height in meters.

^b The Simplified Acute Physiology Score (SAPS) II is calculated from 17 variables at inclusion, information about previous health status, and from information obtained at admission. Scores can range from 0 to 163, with higher scores indicating more severe disease.

^c Sepsis-related Organ Failure Assessment (SOFA) score range from 0 to 24, with higher scores indicating more severe organ failure.

^d MACOCHA is calculated from 7 variables including Mallampati score III or IV, apnoea syndrome, cervical spine limitation, opening mouth less than 3 cm, coma, hypoxia, non-trained operator. Score range from 0 to 12 points, with higher scores indicating risk of difficult intubation.

^e Cormack grade III, if no part of the glottis can be seen, but only the epiglottis, grade IV, if not even the epiglottis can be exposed.

^f The Intubation Difficulty Scale denotes the Intubation Difficulty Scale score, 0 easy, 0 to 5 slight difficulty, >5 moderate to major difficulty for intubation.

Table 2: Primary and Secondary outcomes in the Intention-to-Treat Population according to the Group of Treatment.

Outcome	NIV (n=142)	HFOT (n=171)	Absolute difference estimate (95% CI)	p value
Primary outcome:				
SpO ₂ <80% during intubation procedure				
Number of patients	33	47	-4.2 (-13.7; 5.5)	0.39
% of patients (95% CI)	23 (17-31)	27 (21-35)		
Secondary Outcomes				
Lowest SpO ₂ during intubation procedure, %	87±13	84±16	3.0 (-0.3; 6.3)	0.13
SpO ₂ at the beginning of preoxygenation, %	95±5	95±4	0.0 (-1.0; 1.0)	0.65
SpO ₂ at the end of preoxygenation, %	97±4	96±5	1.0 (0.0; 2.0)	0.08
Duration of laryngoscopy, n (%)				0.86
< 1 min	88 (63)	105 (61)	1.4 (-9.3; 12.1)	
1 to 3 min	40 (29)	53 (31)	-2.4 (-12.4; 7.8)	
> 3 min	12 (9)	13 (8)	1.0 (-5.2; 7.6)	
Procedure of tracheal intubation, n (%)				0.75
Number of laryngoscopy attempt				
One	113 (80)	135 (79)	0.6 (-8.5; 9.5)	
Two	22 (15)	30 (17)	-2.0 (-10.2; 6.4)	
Three or more, or >10 minutes	7 (5)	6 (4)	1.4 (-3.2; 6.7)	
First operator junior	26 (18)	37 (22)	-3.3 (-12.0; 5.7)	0.46
Intervention of another skilled operator	38 (27)	47 (27)	-0.7 (-10.4; 9.2)	0.89
Use of alternative management devices	16 (11)	25 (15)	-3.3 (-10.7; 4.4)	0.38
Introducer	15 (11)	22 (13)	-2.3 (-9.4; 5.1)	
Other	2 (1)	6 (4)	-2.1 (-6.2; 1.9)	
Successful intubation, n (%)	142 (100)	171 (100)	0.0 (0.0;0.0)	—
At least one episode of systolic arterial pressure <90 mm Hg, n (%)	70 (50)	86 (47)	-1.0 (-12.0; 10.0)	0.86
Serious events				
Immediate complications, n (%)				
At least one episode of systolic arterial pressure <90 mm Hg	70 (49)	86 (50)	-1.0 (-12.0; 10.0)	0.86
Sustained cardiac arrhythmia	3 (2)	3 (2)	0.4 (-3.2; 4.4)	0.99
Bradycardia	2 (1)	3 (2)	-0.3 (-3.8;3.4)	0.81
Cardiac arrest during and after intubation	1 (1)	5 (5)	-3.2 (-6.0; 13.7)	0.23
Esophageal intubation	8 (6)	6 (4)	2.1 (-2.7; 7.5)	0.42
Regurgitation	0 (0)	2 (1)	-1.1 (-4.2; 1.6)	0.50
Gastric distension	11 (8)	6 (4)	4.2 (-0.9; 10.1)	0.12
Dental injury	0 (0)	1 (1)	-0.6 (-3.2; 2.1)	0.99
Agitation	1 (0.7)	0 (0)	0.7 (-1.6; 3.9)	0.45
New infiltrate on chest-ray after intubation	28 (19)	33 (19)	0.4 (-8.3; 9.4)	0.96
Late complications, n (%)				
Ventilator-associated pneumonia within day 7	21 (15)	18 (11)	4.3 (-3.1; 12.0)	0.26
Ventilator-associated pneumonia during ICU stay	31 (22)	35 (20)	1.4 (-7.6; 10.6)	0.77
Death at day 28	53 (37)	58 (34)	3.4 (-7.1; 14.0)	0.53
Late outcomes				
SOFA score at Day 1, points	8±4	8±4	0.0 (-0.9; 0.9)	0.62
SOFA score at Day 7, points	5±4	5±3	0.0 (-0.8; 0.8)	0.82
Ventilator-associated pneumonia within day 7, n (%)	21 (15)	18 (10)	4.3 (-3.1; 12.0)	0.30
Duration of mechanical ventilation, days	9±10	10±10	-1.0 (-2.6; 0.6)	0.47
ICU length of stay, days	13±10	12±9	1.0 (-1.1; 3.1)	0.82

The data are means ± SD, or absolute numbers (%).

Abbreviations: NIV, non-invasive ventilation; HFOT, high flow nasal cannula oxygen therapy; SpO₂, pulse oximetry; CI, confident interval; SD, standard deviation; SOFA, Sepsis-related Organ Failure Assessment; ICU, intensive care unit.

Table 3: Primary and Secondary Outcomes in the Intention-to-Treat population According to the Sub-group of Stratification and Group of Treatment.

	Severe-to-moderate hypoxemia (PaO ₂ :FiO ₂ ≤200 mm Hg)				Mild hypoxemia (PaO ₂ :FiO ₂ >200 mm Hg)			
	NIV (n=117)	HFOT (n=125)	Absolute difference estimate (95% CI)	p value	NIV (n=25)	HFOT (n=46)	Absolute difference Estimate (95% CI)	p value
Primary outcome:								
SpO ₂ < 80% during intubation procedure	28	44		0.0553	5	3		0.1197
% of patients (95% CI)	24 (16-32)	35 (27-44)	-11.3 (-22.3; 0.3)		20 (4-36)	7 (0-14)	13.4 (-2.2; 33.1)	
Adjusted on PaO ₂				0.0459				0.1003
Secondary Outcomes								
SpO ₂ at the beginning of preoxygenation, %	94±5	94±4	0.0 (-1.1; 1.1)	0.75	97±3	97±4	0.0 (-1.8; 1.8)	0.36
SpO ₂ at the end of preoxygenation,	97±4	96±6	1.0 (-0.0; 2.0)	0.02	99±3	98±4	1.0 (-0.8; 2.8)	0.31
Lowest SpO ₂ during intubation procedure, %	86±12	81±17	5.0 (1.2; 8.7)	0.02	90±15	93±8	-3.0 (-8.4; 2.4)	0.31

The data are means ± SD, or absolute numbers (%).

Abbreviations: NIV, non-invasive ventilation; HFOT, high flow nasal cannula oxygen therapy; SpO₂, pulse oximetry; CI, confident interval; SD, standard deviation; SOFA, Sepsis-related Organ Failure Assessment; ICU, intensive care unit.