BMJ Open

A new method of preoxygenation for orotracheal intubation in hypoxemic acute respiratory failure patients in intensive care unit, noninvasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011298
Article Type:	Protocol
Date Submitted by the Author:	27-Jan-2016
Complete List of Authors:	Jaber, S.; Saint-Eloi Hospital, University Teaching Hospital of Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B); INSERM U1046 MOLINARI, Nicolas; University of Montpellier Lapeyronie Hospital, Department of Statistics, UMR 729 MISTEA DE JONG, Audrey; Saint-Eloi Hospital, University Teaching Hospital of Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B); INSERM U1046
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia, Emergency medicine, Medical management
Keywords:	Adult intensive & critical care < ANAESTHETICS, Adult thoracic medicine < THORACIC MEDICINE, Respiratory physiology < THORACIC MEDICINE

Study protocol

A new method of preoxygenation for orotracheal intubation in hypoxemic acute respiratory failure patients in intensive care unit, noninvasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol

Samir Jaber,[1,2] Nicolas Molinari,[3] Audrey De Jong[1,2]

[1]Department of Anaesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France

[2] INSERM U1046 Montpellier, France

[3] Department of Statistics, University of Montpellier Lapeyronie Hospital, UMR 729 MISTEA, Montpellier, France

Correspondence: Pr Samir JABER, Intensive Care Unit & Anaesthesiology Department, University of Montpellier Saint-Eloi Hospital. Montpellier, France; 80 avenue Augustin Fliche. 34295 Montpellier Cedex 5, France
Tel: 00. 33. 467. 337. 271; Fax: 00. 33. 467.337. 448; E-mail: s-jaber@chu-montpellier.fr

Abstract

Introduction: Tracheal intubation in the intensive care unit (ICU) is associated with severe life-threatening complications including severe hypoxemia. Preoxygenation before intubation has been recommended in order to decrease such complications. Non invasive ventilation (NIV)-assisted preoxygenation allows increased oxygen saturation during intubation procedure, by applying a positive-end expiratory pressure (PEEP) to prevent alveolar derecruitment. However, the NIV-mask has to be taken off after preoxygenation to allow the passage of the tube through the mouth. The hypoxemic patient does not receive oxygen during this period, at risk of major hypoxemia. High-flow nasal cannula oxygen (HFNC) has a potential of apnoeic oxygenation during the apnoea period following the preoxygenation with NIV. Whether application of HFNC combined with NIV is more effective at reducing oxygen desaturation during the intubation procedure compared to NIV alone for preoxygenation in hypoxemic ICU patients with acute respiratory failure remains to be established.

Methods and analysis: The HFNC combined to NIV for decreasing oxygen desaturation during the intubation procedure in ICU hypoxemic patients (OPTINIV) trial is an investigator-initiated monocenter randomised controlled two-arm trial with assessor-blinded outcome assessment. The OPTINIV trial randomises 50 hypoxemic patients requiring orotracheal intubation for acute respiratory failure to receive NIV (Pressure support=10, PEEP=5, inspired fraction of oxygen (FiO2)=100%) combined with HFNC (Flow=60L/min, FiO2=100%, interventional group) or NIV alone (reference group) for preoxygenation. The primary outcome is lowest oxygen saturation during the intubation procedure. Secondary outcomes are intubation-related complications, quality of preoxygenation and ICU mortality.

Ethics and dissemination: The study project has been approved by the appropriate ethics committee (CPP Sud-Méditerranée). Informed consent is required. If combined application of HFNC and NIV for preoxygenation of ICU hypoxemic patients proves superior to NIV preoxygenation, its use will become standard practice, thereby decreasing hypoxemia during intubation procedure and potentially complications related to intubation.

Trial registration: ClinicalTrials.gov Identifier: NCT02530957.

Strengths and limitations of the study: Strengths of the study are the blinded assessment. and the inclusions performed around the clock, nights and week-end included as a routine clinical practice. Limitations of the study are that the operator performing intubation can be aware of the group of inclusion. However, the assessor is an independent observer, who

does not know the group of inclusion. Some could highlight the risk of gastric air insufflation and aspiration related to positive airway pressure of NIV as a method of preoxygenation. However, as previously reported and in the present study, it will be recommended to never exceed a total insufflation airway pressure (PS+PEEP) of 15 cmH2O which has been shown to be safe to avoid gastric air insufflation.

Keywords: Preoxygenation, non invasive ventilation, oxygen therapy, complications related to intubation, acute respiratory failure, intensive care unit, critical care

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

Patients admitted to Intensive Care Units (ICU) often require respiratory support. Hypoxemia and cardiovascular collapse are the initial and most serious life-threatening complications associated with difficult airway access, both during emergency intubation in the critically ill[2-6] and in planned intubations (e. g., scheduled surgery or invasive procedures).[7 8] ICU intubation conditions are worse than intubation conditions in operative rooms.[4 9] A non planned and urgent intubation procedure, severity of patient disease and ergonomic issues explain the morbidity associated with intubation in ICU. To prevent and limit the incidence of severe hypoxemia following intubation and its complications, several pre-oxygenation techniques and intubation algorithms have been developed ,[3 5 10 11] and specific risk factors for difficult intubation in ICU have been identified, constituting the MACOCHA score (Mallampati score III or IV, obstructive sleep Apnoea syndrome, reduced mobility of Cervical spine, limited mouth Opening < 3 cm, Coma, severe Hypoxemia (<80%) and non Anaesthesiologist status).[2]

Noninvasive ventilation (NIV) for preoxygenation of patients with hypoxemic acute respiratory failure is associated with less hypoxemia than preoxygenation with nonrebreather bag-valve mask during intubation procedure.[12] Indeed, associating Pressure Support (PS) with Positive end expiratory pressure (PEEP) limits alveolar collapse and atelectasis formation, responsible for hypoventilation and low perfusion ventilation ratio.[8 13] Incidence of severe hypoxemia defined by a pulse oxymetry (SpO2) of less than 80% can be decreased by applying NIV preoxygenation, a method which is now used by many teams for preoxygenation of patients with hypoxemic acute respiratory failure.

However, although NIV can be safely applied for preoxygenation before intubation procedure, NIV mask has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. Furthermore, positioning the orotracheal tube into the trachea may take time, from a few seconds to several minutes in case of difficult

intubation. The hypoxemic patient does not receive oxygen during this period, which participates in the risk of severe hypoxemia during intubation.

High-flow nasal cannula oxygen therapy (HFNC), which delivers high flow heated and humidified oxygen and air via nasal prongs at a prescribed fraction of inspired oxygen (FiO2) and a maximum flow of 60 L/min,[14-17] can be continued during the passage of orotracheal tube through the mouth. Apnoeic oxygenation maintains blood oxygenation for a significant period of time in breathless conditions.[18] Recent studies suggest that HFNC could allow apnoeic oxygenation,[16 19 20] and as a consequence could be interestingly used to continue blood oxygenation during the apnoea period of intubation, especially when the NIV mask is removed. Furthermore, previous studies have shown that HFNC oxygen therapy generates a flow-dependent positive airway pressure and improves oxygenation by increasing end-expiratory lung volume,[21] thus suggesting possible associated alveolar recruitment . However, the patients' mouth must be closed to observe this effect ,[22] suggesting that NIV could be more efficient than HFNC to prevent alveolar derecruitment.

Using HFNC combined with NIV may have potential advantages over conventional NIV alone for preoxygenation before intubation in hypoxemic ICU patients. Some studies have assessed the preoxygenation effect of HFNC compared to facial mask or other devices, with conflicting results.[16 17 23] However, the technique of preoxygenation associating NIV and HFNC, respectively combining the concepts of prevention of alveolar derecruitment and of apnoeic oxygenation, has never been assessed and benefit remains to be established.

Objectives

Primary objective. To determine whether application of HFNC combined with NIV is more effective at reducing oxygen desaturation during intubation procedure over NIV alone for preoxygenation in ICU patients needing mechanical ventilation for hypoxemic acute respiratory failure.

Secondary objectives. To determine whether in comparison to NIV alone, application of HFNC combined to NIV could provide a better preoxygenation quality, less complications related to intubation, decrease in ICU morbidity and mortality day-28 rate.

The OPTINIV study aims to compare the effects of preoxygenation with a combination of NIV and HFNC delivered together compared with NIV alone on lowest oxygen saturation during intubation procedure and complications related to intubation of ICU hypoxemic patients needing mechanical ventilation for hypoxemic acute respiratory failure.

The hypothesis is that preoxygenation combining NIV and HFNC compared to NIV alone could prevent desaturation during the intubation procedure.

Trial design

The HFNC (Optiflow®, Fisher & Paykel Healthcare, Auckland, NZ) combined to NIV for decreasing oxygen desaturation during the intubation procedure in ICU hypoxemic patients (OPTINIV) trial is an investigator initiated single center randomised controlled two-arm trial.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the OPTINIV trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The OPTINIV study is taking place in a mixed medical and surgical 16-bed ICU, in France.

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU and require mechanical ventilation through an orotracheal tube. Hypoxemic acute respiratory failure is defined as a respiratory rate higher than 30 per minute and a FiO2 requirement of 50% or more to obtain at least 90% oxygen saturation, and an estimated arterial oxygen tension to fraction inspired in oxygen (PaO2/FiO2 ratio) below 300 mmHg, in the 4 hours before inclusion.[17]

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included:

age <18 years, pregnant or breastfeeding woman, protected person, intubation in case of cardio circulatory arrest, nasopharyngeal obstacle contraindicating the use of HFNC and usual contraindications to NIV.[24]

Interventions

Patients eligible for inclusion will be randomly assigned to the interventional group or to the reference group (Figure 2). The interventional group consists in applying preoxygenation at 30 degrees of head-up inclination with NIV (PS of 10 cmH2O, PEEP of 5cm H2O, FiO2 = 100%, inspiratory flow trigger at 0,3L/min, expiratory trigger at 25%, maximal inspiratory time at 1.5 s) and HFNC (humidified oxygen flow of 60L/min, FiO2 = 100%, Figure 3A.). We will use an ICU ventilator with NIV software (Evita V500 or XL, Drager Lubeck). The reference group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV only (same parameters as in the interventional group) without HFNC (nasal cannula positioned without any flow, Figure 3B.). The ventilator circuit will be connected to a standard soft style manual resuscitator face mask, with a capnograph inserted between face mask and flow sensor. During preoxygenation, the operator will ensure the jaw is pulled forward with a two-handed thenar eminence grip. After general anaesthetic induction, the NIV mask will be removed, enabling laryngoscopy vision. No ventilation will be performed during the apnoea. The nasal cannula will be maintained during the laryngoscopic procedure.

Outcomes

Primary outcome measure

Primary outcome variable is the lowest oxygen saturation indicated by SpO2 during the intubation procedure. The intubation procedure lasts from the beginning of the first laryngoscopy (the end of rapid sequence induction) to the confirmation of the orotracheal intubation by capnography after the patient is connected to mechanical ventilation.[17]

Secondary outcome measures

Secondary outcome variables are preoxygenation quality (duration, ability to improve SpO2, proportion of patients in whom it is impossible to obtain a saturation > 90% during preoxygenation), complications related to intubation (severe: severe hypoxemia defined by lowest saturation < 80 %, severe cardiovascular collapse, defined as systolic blood pressure less than 65 mm Hg recorded at least once or less than 90 mm Hg lasting 30 minutes despite 500–1,000 ml of fluid loading (crystalloids solutions) or requiring introduction or increasing doses by more than 30% of vasoactive support, cardiac arrest, death during intubation; moderate: difficult intubation, severe ventricular or supraventricular arrhythmia requiring intervention, oesophageal intubation, agitation, pulmonary aspiration, dental injuries), morbidity in ICU (ICU length of stay, invasive ventilator-free days and mortality rate on day 28).

A previous trial showed that preoxygenation using NIV was more effective at reducing arterial oxyhemoglobin lowest saturation than the usual method.[12] Therefore, the study protocol stresses that NIV must be used as the reference group in the OPTINIV trial, as stated by the unit protocols,[3 5] which are followed for each intubation procedure. Other pre-intubation procedures included in the unit protocols consist of fluid loading if there is no cardiogenic edema, preparation of sedation by the nursing team and presence of two operators. The availability of equipment for management of a difficult airway will be checked. During the procedure, the patient will be ventilated in case of desaturation to less than 80 %. In case of inadequate ventilation and unsuccessful intubation, emergency non-invasive airway ventilation (supraglottic airway) will be used. The difficulty of intubation will be assessed using the MACOCHA score.[2] If a difficult intubation is predicted (MACOCHA score ≥ 3), the use of a malleable stylet and of videolaryngoscopy or combo videolaryngoscopy will be recommended. In cases of abundant secretions even after aspiration, direct laryngoscopy will be preferred rather than videolaryngoscopy. Finally, in cases of intubation failure, an intubating stylet (malleable stylet or long flexible angulated stylet) will be added first, followed successively by the use of videolaryngoscopy if not initially used, an intubation laryngeal mask airway, fiberoscopy and finally the use of rescue percutaneal or surgical airway. The

rapid sequence induction of general anaesthesia for orotracheal intubation under laryngoscopy will be used according to the unit protocol,[5] with a Sellick maneuver,[25] a hypnotic drug (Ketamine 2,5 mg/kg) in the absence of contraindications and a neuromuscular blocker (either Suxamethonium 1 mg/kg in the absence of allergy and other contraindications such as hyperkalliemia, burns, rhabdomyolysis, neuromuscular disease, or Rocuronium 1 mg/kg). A metal blade will be used.[26] Just after intubation (post-intubation period), the tube's position will be checked by capnography, long-term sedation will be initiated as soon as possible (to avoid agitation)[5] and 'protective' mechanical ventilation settings will be used, as defined by the acute respiratory distress syndrome network.[27] At any time, vasopressors will be mandatory in the event of severe hemodynamic collapse.

Participant timeline

The participant timeline is described in Table 1.

Sample size

The primary outcome is the lowest oxygen saturation during intubation procedure. For this study, 2 × 23 patients are needed to detect a 5% difference in the lowest oxygen saturation during intubation procedure, with a standard deviation of 6%, at a two-sided α level of 0.05 and a statistical power of 80%.[4 10 12] To take into account withdrawn consent after randomisation, inclusions not meeting the inclusion criteria or improvement before intubation, 25 patients will be included in each group.

Recruitment

Patients are expected to be included during a one-year inclusion period starting July 2015.

2015: Protocol, approvals from ethics committee, and trial tool development (case report form, randomisation system).

2015 to 2016: Inclusion of patients.

2016: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

A computer-generated randomisation will be used, which will be generated by a statistician who is not involved in determination of patient eligibility or outcome assessment. Randomisation will be accomplished by using opaque sealed envelopes. The randomisation envelopes will contain a card stating the group to which the patient was randomised.

Blinding

The study will be blinded to the observer collecting data (Figure 3). NIV will be performed and nasal cannula positioned in both groups, to allow blinding. The operator performing the intubation will blind the group by placing a large sheet over the oxygen flow meter (Figure 3). In the interventional group (called A. Real HFNC+NIV in the figure 3), the nasal cannula will be connected to the oxygen flow meter via a tube and oxygen set at 60L/min and 100% of FiO2. In the reference group (called B. Fake HFNC+NIV in the figure 3), the tube connected to the nasal cannula positioned on the patient will be hidden under the sheet, without connection to the oxygen flow meter. No flow of oxygen will be administered by the nasal cannula in the reference group. To mimic the noise of HFNC in the reference group, another nasal cannula will be hidden under the sheet and connected to the oxygen flow meter, with a flow also set at 60L/min delivered in the room atmosphere (Figure 3). The blinded observer will be one of the ICU residents, a nurse or a member of the trained local research team.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on case report forms by trained local research coordinators or residents, blinded to the randomised intervention. Patients will receive standard intensive care unit monitoring consisting of electrocardiogram analysis, SpO2, and a noninvasive blood pressure cuff. Prior to orotracheal intubation, the nurse will set the time intervals on the noninvasive blood pressure cuff monitoring and electronic medical record in

the patient's room to run every minute until 15 minutes after successful intubation. Continuously throughout the procedure (from preoxygenation to one hour following intubation) vital parameters will be collected by a software on an external laptop called S5/Collect by General Electric, on the General Electric Carescape monitors.

The following data will be collected and registered before intubation: demographic and epidemiologic data : age, sex, weight, height, date and hour of intubation, on-call procedure, severity scores (Simplified Acute Physiologic Score (SAPS) II at admission, Sequential Organ Failure Assessment (SOFA) score on the day of the procedure), type of admission, reason of ICU admission, indication of intubation, co morbidities. The following parameters will be recorded during the four hours before intubation: nature and number of operators, and their training, arterial pressure and lowest saturation, arterial blood gases with calculated PaO2/FiO2 ratio, delay between the time where the intubation is decided and its realization, presence of vasopressor drugs, prior NIV use, existence of predictive criteria of difficult intubation evaluated by the MACOCHA score.[2]

During preoxygenation, the following data will be recorded: the length of preoxygenation, the vital parameters (oxygen saturation at the beginning and at the end of the preoxygenation, lowest oxygen saturation, lowest and highest arterial pressure and heart rate).

During the intubation procedure, the following parameters will be collected : doses of hypnotic and neuromuscular blocker used, oxygen saturation at the beginning and at the end, lowest oxygen saturation, mild (<90%), moderate (<85%) or severe (<80%) hypoxemia, total duration of the intubation procedure, number of operators, number of attempts, Cormack grade, traction force on the laryngoscope, Sellick maneuver, difficult intubation (more than 2 attempts), modified Intubation Difficulty Scale (IDS score)[28] and occurrence of complications related to intubation.

After the intubation procedure (until one hour after): arterial blood gases with calculated PaO2/FiO2 ratio will be performed at 5-min and 30-min. Complications occurring

will be collected: cardiac arrest, arrhythmias, pneumothorax, arterial hypotension, hypoxemia, agitation, death.

From postoperative day 1 to day 28 will be assessed: morbi-mortality by the length of mechanical ventilation, the length of stay in ICU and the mortality at day 28.

Statistical methods

Statistical analysis

A predefined statistical analysis plan will be followed. The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention to-treat population, including all the randomised patients except patients who withdraw their consent, do not meet the inclusion criteria or improve before intubation. All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, version 9.3; SAS Institute; Cary, NC, USA, and R, version 2.14.1). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described, using n (%) for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables.

Analysis of the primary outcome

Unpaired t test or the Mann–Whitney U test when appropriate will be used for primary outcome analysis.

Analysis of secondary outcomes

The chi-square test (or Fisher's exact test as appropriate) will be used for secondary binary outcomes. Continuous variables will be compared with the use of the unpaired t test or the Mann–Whitney U test when appropriate.

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICU attended formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the type of preoxygenation used.

Auditing

An independent data and safety monitoring board, composed of three experts (Catherine Paugam, Karim Asehnoune and Emmanuel Futier) will monitor the safety of the trial.

ETHICS AND DISSEMINATION

Research ethics approval

The Institutional Review Board of the University Hospital of Montpellier (France) approved the trial. By May 13 2015, the study has been approved by a central ethics committee (Comité de Protection des Personnes Sud-Méditerranée IV, Montpellier, France) with the registration number IDRCB 2015-A00708-41. The OPTINIV study is conducted in accordance with the declaration of Helsinki and was registered on at http://www.clinicaltrials.gov with trial identification number NCT02530957.

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki. If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of hypoxemia. These patients will be included after written informed consent is provided by next of kin or an emergency procedure (investigator signature) if next of kin is not present. When available, after recovery, patients will be retrospectively asked for written consent to continue the trial.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

DISCUSSION

Intubation in ICU is associated with severe hypoxemia.[2 4] Optimizing preoxygenation is, therefore, of particular importance before the intubation procedure, especially in hypoxemic patients needing mechanical ventilation for acute respiratory failure. However, although NIV preoxygenation is effective to reduce hypoxemia during intubation procedure,[12] NIV mask has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. Association of HFNC to alveolar recruitment by NIV could be of particular interest both for increasing administration of oxygen during preoxygenation, and to allow apnoeic oxygenation during the apnoea period, time where the hypoxemic patient usually receives no oxygen. This period without oxygenation can last several minutes, especially when the intubation is difficult.

The OPTINIV trial is the first randomised controlled study powered to investigate the effectiveness of combined NIV and HFNC to decrease severe hypoxemia during the intubation procedure in hypoxemic acute respiratory failure patients in ICU.

Apnoeic oxygenation is a physiological phenomenon in which, provided that a patent air passageway exists between the lungs and the exterior, the difference between the alveolar rates of oxygen removal and carbon dioxide excretion generates a negative pressure gradient of up to 20 cmH2O that drives oxygen into the lungs.[18 29 30] The aim of apnoeic oxygenation use throughout the intubation procedure is therefore to reduce severe hypoxemia occurrence during intubation procedure.[31] Previous studies assessed the effect of apnoeic oxygenation, with conflicting results. Apnoeic oxygenation increased the time to severe desaturation during the intubation procedure in acute lung injury in an experimental study in piglets.[32] Miguel-Montanes et al.[16] compared 3 minutes of preoxygenation using a face mask to 60 L/min of HFNC in patients with mild-to-moderate hypoxemia. With the face mask, the median lowest SpO2 during intubation was 94% versus 100% with HFNC. Vourc'h et al[17] found no difference on lowest arterial oxygen during intubation in hypoxemic patients between 60L/min of HFNC and 4-minutes of preoxygenation with a face mask (92% vs 90%,

p= 0.44). Semler et al.[23] performed a randomised trial in a medical ICU, enrolling 150 patients. The administration of 15L/min nasal cannula oxygen in the apnoeic oxygenation group was not associated with significantly increased arterial oxygen saturation (from 92% in the apnoeic oxygenation group to 90% in the usual care group (p= 0.16)). The discrepancies between the results of these 3 studies[16 17 23] could mainly be explained by the oxygen flow used for the apnoeic oxygenation group (from 15 to 60 L/min) and the different studied populations in term of hypoxemia. Moreover, the design of these studies differ from the design of the current study, which allows to specifically study apnoeic oxygenation by HFNC simultaneously combined with NIV preoxygenation.

The primary endpoint of the trial is the lowest oxygen saturation during intubation procedure. The incidence of severe hypoxemia following intubation is particularly high in ICU, reaching up to 50%.[2 4] The ability to anticipate hypoxemia occurrence is of critical importance to prevent the development of subsequent complications. Severe hypoxemia can lead to cardiac arrest, neurologic damage, or multiple organ failure.[2] Moreover, since we collect and report on most complications related to intubation, either severe or moderate, it may still be possible to determine the effects of combined preoxygenation on other complications.

One limitation of the study is that the operator performing intubation can be aware of the group of inclusion. However, the assessor is an independent observer, who does not know the group of inclusion. Some could highlight the risk of gastric air insufflation and aspiration related to positive airway pressure of NIV as a method of preoxygenation. However, as previously reported[12 17 26 33] and in the present study, it will be recommended to never exceed a total insufflation airway pressure (PS+PEEP) of 15 cmH2O which has been shown to be safe to avoid gastric air insufflation.[34-36]

One strength of the study is the blinded assessment (see above, Figure 3). Moreover, the inclusions will be performed around the clock, nights and week-end included as a routine clinical practice.

In conclusion, the OPTINIV trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that NIV combined to HFNC in comparison to NIV alone allows to decrease severe hypoxemia during the intubation procedure of hypoxemic ICU patients requiring mechanical ventilation for acute respiratory failure. The OPTINIV trial will also assess the effects of combined NIV and HFNC for preoxygenation on intubation-related complications.

Trial status

The trial is ongoing and is actively enrolling.

Abbreviations

ICU: Intensive Care Unit; NIV: Noninvasive ventilation; PS : Pressure support; PEEP : Positive end expiratory pressure; HFNC: High-flow nasal cannula oxygen therapy; SpO2: pulse oxymetry; FiO2: fraction inspired in oxygen; PaO2/FiO2: Arterial oxygen tension to inspiratory oxygen fraction ratio; SAPS : Simplified Acute Physiologic Score; SOFA : Sequential Organ Failure Assessment

References

1. Chan AW, Tetzlaff JM, Gotzsche PC*, et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
2. De Jong A, Molinari N, Terzi N*, et al.* Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187(8):832-9.
3. De Jong A, Jung B, Jaber S. Intubation in the ICU: we could improve our practice. *Crit Care* 2014;18(2):209.
4. Jaber S, Amraoui J, Lefrant J-Y*, et al.* Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Crit Care Med* 2006;34(9):2355-61.
5. Jaber S, Jung B, Corne P*, et al.* An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive care medicine* 2010;36(2):248-55.
6. Martin LD, Mhyre JM, Shanks AM*, et al.* 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114(1):42-48.
7. Peterson GN, Domino KB, Caplan RA*, et al.* Management of the difficult airway: a closed claims analysis. *Anesthesiology* 2005;103(1):33-39.
8. De Jong A, Futier E, Millot A*, et al.* How to preoxygenate in operative room: Healthy subjects and situations "at risk". *Ann Fr Anesth Reanim* 2014;33(7-8):457-61.
9. De Jong A, Molinari N, Pouzeratte Y*, et al.* Difficult intubation in obese patients: incidence, risk factors, and complications in the operating theatre and in intensive care units. *Br J Anaesth* 2015;114(2):297-306.
10. De Jong A, Clavieras N, Conseil M*, et al.* Implementation of a combo videolaryngoscope for intubation in critically ill patients: a before-after comparative study. *Intensive care medicine* 2013;39(12):2144-52.
11. De Jong A, Molinari N, Conseil M*, et al.* Video laryngoscopy versus direct laryngoscopy for orotracheal intubation in the intensive care unit: a systematic review and meta-analysis. *Intensive care medicine* 2014;40(5):629-39.
12. Baillard C, Fosse J-P, Sebbane M*, et al.* Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med* 2006;174(2):171-77.
13. Jaber S, Michelet P, Chanques G. Role of non-invasive ventilation (NIV) in the perioperative period. *Best practice & research Clinical anaesthesiology* 2010;24(2):253-65.
14. Chanques G, Constantin JM, Sauter M*, et al.* Discomfort associated with underhumidified high-flow oxygen therapy in critically ill patients. *Intensive Care Med* 2009;35(6):996-1003.
15. Chanques G, Jaber S. Unexpected progress of an old intensive care therapy, oxygen: towards more comfort and less mechanical ventilation... *Rev Mal Respir* 2013;30(8):605-8.
16. Miguel-Montanes R, Hajage D, Messika J*, et al.* Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. *Crit Care Med* 2015;43(3):574-83.
17. Vourc'h M, Asfar P, Volteau C*, et al.* High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled clinical trial. *Intensive care medicine* 2015;41(9):1538-48.
18. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. *Anesthesiology* 1959;20:789-98.
19. Patel A, Nouraei SA. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia* 2015;70(3):323-9.

20. Kolettas A, Grosomanidis V, Kolettas V*, et al.* Influence of apnoeic oxygenation in respiratory and circulatory system under general anaesthesia. *Journal of thoracic disease* 2014;6 Suppl 1:S116-45.
21. Futier E, Jaber S. High-flow nasal cannula following extubation: is more oxygen flow useful after surgery? *Intensive care medicine* 2015;41(7):1310-3.
22. Chanques G, Riboulet F, Molinari N*, et al.* Comparison of three high flow oxygen therapy delivery devices: a clinical physiological cross-over study. *Minerva Anestesiol* 2013;79(12):1344-55.
23. Semler M, Janz D, Lentz R*, et al.* Randomized trial of apneic oxygenation during endotracheal intubation of the critically ill. *Am J Respir Crit Care Med* 2015.
24. Jaber S, Chanques G, Jung B. Postoperative noninvasive ventilation. *Anesthesiology* 2010;112(2):453-61.
25. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961;2(7199):404-6.
26. Amour J, Marmion F, Birenbaum A*, et al.* Comparison of plastic single-use and metal reusable laryngoscope blades for orotracheal intubation during rapid sequence induction of anesthesia. *Anesthesiology* 2006;104(1):60-64.
27. Hager DN, Krishnan JA, Hayden DL*, et al.* Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005;172(10):1241-5.
28. Adnet F, Borron SW, Racine SX*, et al.* The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *Anesthesiology* 1997;87(6):1290-97.
29. Bartlett RG, Jr., Brubach HF, Specht H. Demonstration of aventilatory mass flow during ventilation and apnea in man. *J Appl Physiol* 1959;14(1):97-101.
30. Fraioli RL, Sheffer LA, Steffenson JL. Pulmonary and cardiovascular effects of apneic oxygenation in man. *Anesthesiology* 1973;39(6):588-96.
31. De Jong A, Jaber S. Apneic oxygenation for intubation in the critically ill: let's not give up! *Am J Respir Crit Care Med* 2016;In press.
32. Engstrom J, Hedenstierna G, Larsson A. Pharyngeal oxygen administration increases the time to serious desaturation at intubation in acute lung injury: an experimental study. *Crit Care* 2010;14(3):R93.
33. Futier E, Constantin JM, Pelosi P*, et al.* Noninvasive ventilation and alveolar recruitment maneuver improve respiratory function during and after intubation of morbidly obese patients: a randomized controlled study. *Anesthesiology* 2011;114(6):1354-63.
34. Lawes EG, Campbell I, Mercer D. Inflation pressure, gastric insufflation and rapid sequence induction. *Br J Anaesth* 1987;59(3):315-8.
35. Ho-Tai LM, Devitt JH, Noel AG*, et al.* Gas leak and gastric insufflation during controlled ventilation: face mask versus laryngeal mask airway. *Can J Anaesth* 1998;45(3):206-11.
36. Delay JM, Sebbane M, Jung B*, et al.* The effectiveness of noninvasive positive pressure ventilation to enhance preoxygenation in morbidly obese patients: a randomized controlled study. *Anesth Analg* 2008;107(5):1707-13.

Authors' contributions

ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ. NM and ADJ wrote the statistical analysis plan and estimated the sample size. All authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding statement

The study is an investigator-initiated trial. Study promoter is Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Competing interests

Dr. Jaber reports receiving consulting fees from Drager, Hamilton, Maquet and Fisher & Paykel. No potential conflict of interest relevant to this article was reported for other authors.

Table 1. Participant timeline

	Inclusion	Discharge from ICU	Day 28
Informed consent	X		
Eligibility: check inclusion and exclusion criteria	X		
Randomisation	X		
Filling of case report forms	X	X	X
Vital status			X

ICU, Intensive care unit

Figure Legend

Figure 1

Consort diagram of the OPTINIV trial
ABG: Arterial blood gas; NIV : Non invasive ventilation; HFNC : High-flow nasal cannula oxygen therapy; PS : Pressure support; PEEP : Positive end expiratory pressure; FiO2 : Fraction of inspired oxygen.

Figure 2

Study design of the OPTINIV trial
NIV: Noninvasive ventilation; HFNC: High-flow nasal cannula oxygen therapy; PS: Pressure support; PEEP: Positive end expiratory pressure; FiO2: Fraction of inspired oxygen; ICU: Intensive Care Unit.

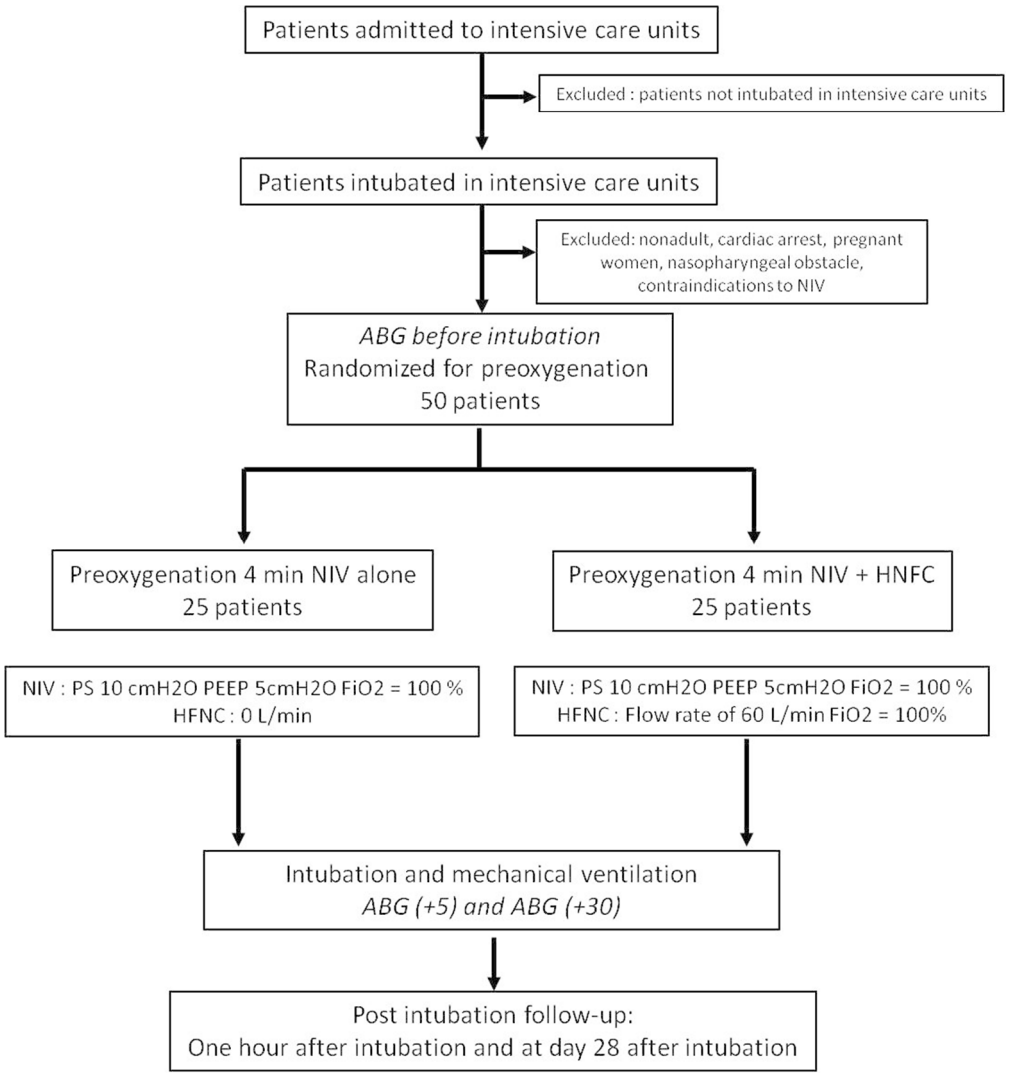
Figure 3

Blinding sequence of the OPTINIV trial
To allow blinding, nasal cannula will be positioned in each group. The operator performing the intubation will blind the group by placing a large sheet over the oxygen flow meter. Both groups will receive VNI.

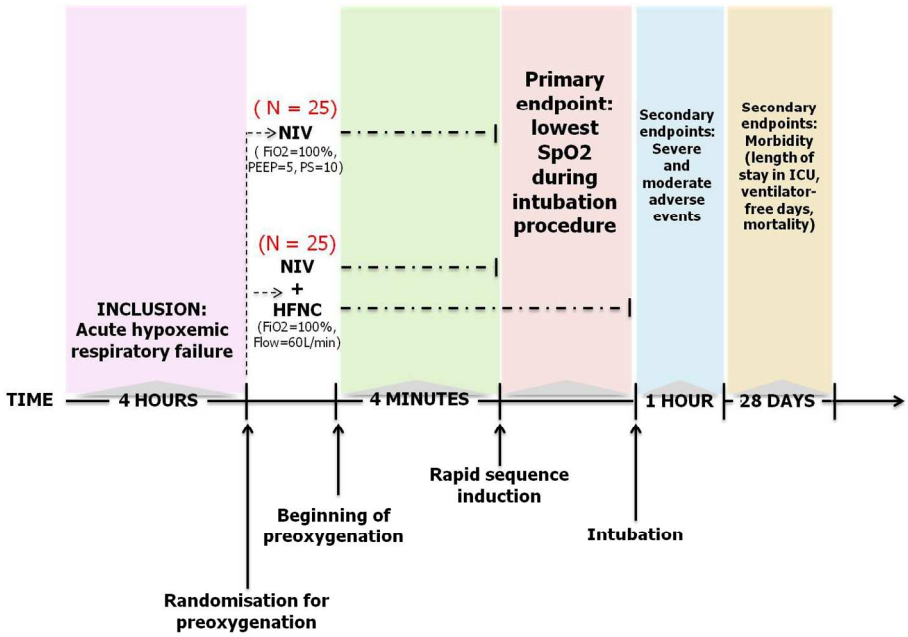
A. Interventional group
In the interventional group (real HFNC+NIV), the nasal cannula will be connected to the oxygen flow meter via a tube and oxygen set at 60L/min and 100% of FiO2 which will be delivered to the patient. The interventional group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV (PS of 10 cmH2O, PEEP of 5cm H2O, FiO2 = 100%) and oxygen HFNC set at 60L/min and 100% of FiO2.

B. Reference group
In the reference group (Fake HFNC+NIV), no oxygen flow will be administered by the nasal cannula to the patient. The tube connected to the nasal cannula positioned on the patient will be hidden under the sheet, without connection to the oxygen flow meter. To mimic the noise of HFNC in the reference group, another nasal cannula will be hidden under the sheet and connected to the oxygen flow meter, with a flow also set at 60L/min.
The reference group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV only (PS of 10 cmH2O, PEEP of 5 cmH2O, FiO2 = 100%) without oxygen HFNC (nasal cannula positioned without any flow).

HFNC: High-flow nasal cannula oxygen therapy; FiO2 : Inspired fraction of oxygen; NIV : Noninvasive ventilation; PS : Pressure support; PEEP : Positive end expiratory pressure



184x197mm (150 x 150 DPI)

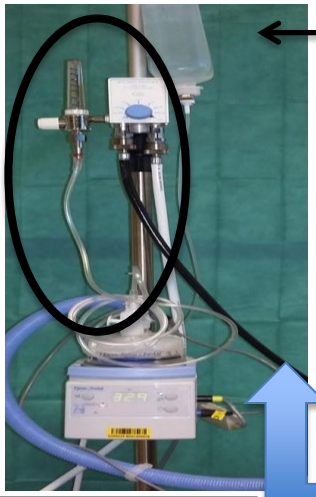


276x175mm (150 x 150 DPI)

FLOW = 60 L/min to the patient
FiO2 = 100 %

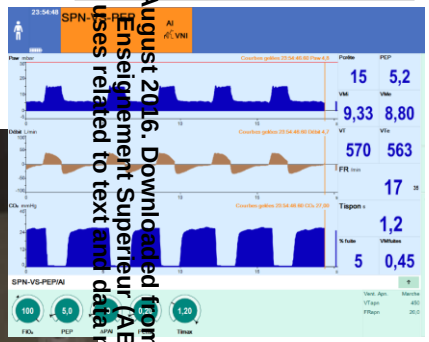
A. Interventional group =
Real HFNC + NIV
(patient received HFNC oxygen flow = 60 L/min)

PS = 10 cm H2O
PEEP = 5 cm H2O
FiO2=100%

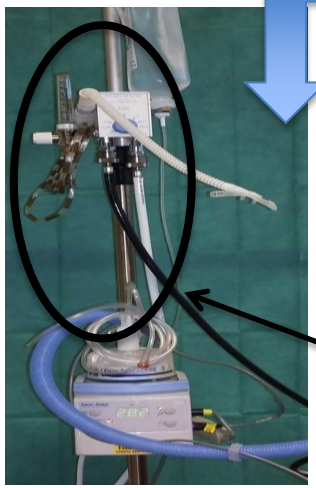


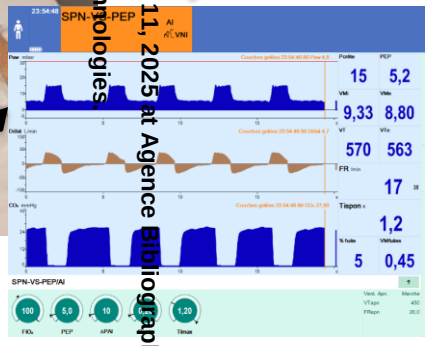
HFNC device blinded

IN BOTH GROUPS
nasal cannula + NIV



NIV screen/ ventilator





B. Reference group =
Fake HFNC + NIV
(patient received HFNC oxygen flow = 0 L/min)

FLOW = 60 L/min to the room atmosphere
FiO2 = 100 %

PS = 10 cm H2O
PEEP = 5 cm H2O
FiO2=100%

BMJ Open

A new method of preoxygenation for orotracheal intubation in hypoxemic acute respiratory failure patients in intensive care unit, noninvasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011298.R1
Article Type:	Protocol
Date Submitted by the Author:	11-Apr-2016
Complete List of Authors:	Jaber, S.; Saint-Eloi Hospital, University Teaching Hospital of Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B); INSERM U1046 MOLINARI, Nicolas; University of Montpellier Lapeyronie Hospital, Department of Statistics, UMR 729 MISTEA DE JONG, Audrey; Saint-Eloi Hospital, University Teaching Hospital of Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B); INSERM U1046
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia, Emergency medicine, Medical management
Keywords:	Adult intensive & critical care < ANAESTHETICS, Adult thoracic medicine < THORACIC MEDICINE, Respiratory physiology < THORACIC MEDICINE

Study protocol

A new method of preoxygenation for orotracheal intubation in hypoxemic acute respiratory failure patients in intensive care unit, noninvasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol

Samir Jaber,[1,2] Nicolas Molinari,[3] Audrey De Jong[1,2]

[1]Department of Anaesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France

[2] INSERM U1046 Montpellier, France

[3] Department of Statistics, University of Montpellier Lapeyronie Hospital, UMR 729 MISTEA, Montpellier, France

Correspondence: Pr Samir JABER, Intensive Care Unit & Anaesthesiology Department, University of Montpellier Saint-Eloi Hospital. Montpellier, France; 80 avenue Augustin Fliche. 34295 Montpellier Cedex 5, France
Tel: 00. 33. 467. 337. 271; Fax: 00. 33. 467.337. 448; E-mail: s-jaber@chu-montpellier.fr

Abstract

Introduction: Tracheal intubation in the intensive care unit (ICU) is associated with severe life-threatening complications including severe hypoxemia. Preoxygenation before intubation has been recommended in order to decrease such complications. Non invasive ventilation (NIV)-assisted preoxygenation allows increased oxygen saturation during intubation procedure, by applying a positive-end expiratory pressure (PEEP) to prevent alveolar derecruitment. However, the NIV-mask has to be taken off after preoxygenation to allow the passage of the tube through the mouth. The hypoxemic patient does not receive oxygen during this period, at risk of major hypoxemia. High-flow nasal cannula oxygen (HFNC) has a potential of apnoeic oxygenation during the apnoea period following the preoxygenation with NIV. Whether application of HFNC combined with NIV is more effective at reducing oxygen desaturation during the intubation procedure compared to NIV alone for preoxygenation in hypoxemic ICU patients with acute respiratory failure remains to be established.

Methods and analysis: The HFNC combined to NIV for decreasing oxygen desaturation during the intubation procedure in ICU hypoxemic patients (OPTINIV) trial is an investigator-initiated monocenter randomised controlled two-arm trial with assessor-blinded outcome assessment. The OPTINIV trial randomises 50 hypoxemic patients requiring orotracheal intubation for acute respiratory failure to receive NIV (Pressure support=10, PEEP=5, inspired fraction of oxygen (FiO2)=100%) combined with HFNC (Flow=60L/min, FiO2=100%, interventional group) or NIV alone (reference group) for preoxygenation. The primary outcome is lowest oxygen saturation during the intubation procedure. Secondary outcomes are intubation-related complications, quality of preoxygenation and ICU mortality.

Ethics and dissemination: The study project has been approved by the appropriate ethics committee (CPP Sud-Méditerranée). Informed consent is required. If combined application of HFNC and NIV for preoxygenation of ICU hypoxemic patients proves superior to NIV preoxygenation, its use will become standard practice, thereby decreasing hypoxemia during intubation procedure and potentially complications related to intubation.

Trial registration: ClinicalTrials.gov Identifier: NCT02530957.

Strengths and limitations of the study: Strengths of the study are the blinded assessment. and the inclusions performed around the clock, nights and week-end included as a routine clinical practice. Limitations of the study are that the operator performing intubation can be aware of the group of inclusion. However, the assessor is an independent observer, who

does not know the group of inclusion. Some could highlight the risk of gastric air insufflation and aspiration related to positive airway pressure of NIV as a method of preoxygenation. However, as previously reported and in the present study, it will be recommended to never exceed a total insufflation airway pressure (PS+PEEP) of 15 cmH2O which has been shown to be safe to avoid gastric air insufflation.

Keywords: Preoxygenation, non invasive ventilation, oxygen therapy, complications related to intubation, acute respiratory failure, intensive care unit, critical care

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

Patients admitted to Intensive Care Units (ICU) often require respiratory support. Hypoxemia and cardiovascular collapse are the initial and most serious life-threatening complications associated with difficult airway access, both during emergency intubation in the critically ill[2-6] and in planned intubations (e. g., scheduled surgery or invasive procedures).[7 8] ICU intubation conditions are worse than intubation conditions in operative rooms.[4 9] A non planned and urgent intubation procedure, severity of patient disease and ergonomic issues explain the morbidity associated with intubation in ICU. To prevent and limit the incidence of severe hypoxemia following intubation and its complications, several pre-oxygenation techniques and intubation algorithms have been developed ,[3 5 10 11] and specific risk factors for difficult intubation in ICU have been identified, constituting the MACOCHA score (Mallampati score III or IV, obstructive sleep Apnoea syndrome, reduced mobility of Cervical spine, limited mouth Opening < 3 cm, Coma, severe Hypoxemia (<80%) and non Anaesthesiologist status).[2]

Noninvasive ventilation (NIV) for preoxygenation of patients with hypoxemic acute respiratory failure is associated with less hypoxemia than preoxygenation with nonrebreather bag-valve mask during intubation procedure.[12] Indeed, associating Pressure Support (PS) with Positive end expiratory pressure (PEEP) limits alveolar collapse and atelectasis formation, responsible for hypoventilation and low perfusion ventilation ratio.[8 13] Incidence of severe hypoxemia defined by a pulse oxymetry (SpO2) of less than 80% can be decreased by applying NIV preoxygenation, a method which is now used by many teams for preoxygenation of patients with hypoxemic acute respiratory failure.[2]

However, although NIV can be safely applied for preoxygenation before intubation procedure, NIV mask has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. Furthermore, positioning the orotracheal tube into the trachea may take time, from a few seconds to several minutes in case of difficult

intubation. The hypoxemic patient does not receive oxygen during this period, which participates in the risk of severe hypoxemia during intubation.

High-flow nasal cannula oxygen therapy (HFNC), which delivers high flow heated and humidified oxygen and air via nasal prongs at a prescribed fraction of inspired oxygen (FiO2) and a maximum flow of 60 L/min,[14-17] can be continued during the passage of orotracheal tube through the mouth. Apnoeic oxygenation maintains blood oxygenation for a significant period of time in breathless conditions.[18] Recent studies suggest that HFNC could allow apnoeic oxygenation,[16 19 20] and as a consequence could be interestingly used to continue blood oxygenation during the apnoea period of intubation, especially when the NIV mask is removed. Furthermore, previous studies have shown that HFNC oxygen therapy generates a flow-dependent positive airway pressure and improves oxygenation by increasing end-expiratory lung volume,[21] thus suggesting possible associated alveolar recruitment . However, the patients' mouth must be closed to observe this effect ,[22] suggesting that NIV could be more efficient than HFNC to prevent alveolar derecruitment.

Using HFNC combined with NIV may have potential advantages over conventional NIV alone for preoxygenation before intubation in hypoxemic ICU patients. Some studies have assessed the preoxygenation effect of HFNC compared to facial mask or other devices, with conflicting results.[16 17 23] However, the technique of preoxygenation associating NIV and HFNC, respectively combining the concepts of prevention of alveolar derecruitment and of apnoeic oxygenation, has never been assessed and benefit remains to be established.

Objectives

Primary objective. To determine whether application of HFNC combined with NIV is more effective at reducing oxygen desaturation during intubation procedure over NIV alone for preoxygenation in ICU patients needing mechanical ventilation for hypoxemic acute respiratory failure.

Secondary objectives. To determine whether in comparison to NIV alone, application of HFNC combined to NIV could provide a better preoxygenation quality, less complications related to intubation, decrease in ICU morbidity and mortality day-28 rate.

The OPTINIV study aims to compare the effects of preoxygenation with a combination of NIV and HFNC delivered together compared with NIV alone on lowest oxygen saturation during intubation procedure and complications related to intubation of ICU hypoxemic patients needing mechanical ventilation for hypoxemic acute respiratory failure.

The hypothesis is that preoxygenation combining NIV and HFNC compared to NIV alone could prevent desaturation during the intubation procedure.

Trial design

The HFNC (Optiflow®, Fisher & Paykel Healthcare, Auckland, NZ) combined to NIV for decreasing oxygen desaturation during the intubation procedure in ICU hypoxemic patients (OPTINIV) trial is an investigator initiated single center randomised controlled two-arm trial.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the OPTINIV trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The OPTINIV study is taking place in a mixed medical and surgical 16-bed ICU, in France.

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU and require mechanical ventilation through an orotracheal tube. Hypoxemic acute respiratory failure is defined as a respiratory rate higher than 30 per minute and a FiO2 requirement of 50% or more to obtain at least 90% oxygen saturation, and an estimated arterial oxygen tension to fraction inspired in oxygen (PaO2/FiO2 ratio) below 300 mmHg, in the 4 hours before inclusion.[17]

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included:

age <18 years, pregnant or breastfeeding woman, protected person, intubation in case of cardio circulatory arrest, nasopharyngeal obstacle contraindicating the use of HFNC and usual contraindications to NIV.[24]

Interventions

Patients eligible for inclusion will be randomly assigned to the interventional group or to the reference group (Figure 2). The interventional group consists in applying preoxygenation at 30 degrees of head-up inclination with NIV (PS of 10 cmH2O, PEEP of 5cm H2O, FiO2 = 100%, inspiratory flow trigger at 0,3L/min, expiratory trigger at 25%, maximal inspiratory time at 1.5 s) and HFNC (humidified oxygen flow of 60L/min, FiO2 = 100%, Figure 3A.). We will use an ICU ventilator with NIV software (Evita V500 or XL, Drager Lubeck). The reference group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV only (same parameters as in the interventional group) without HFNC (nasal cannula positioned without any flow, Figure 3B.). The ventilator circuit will be connected to a standard soft style manual resuscitator face mask, with a capnograph inserted between face mask and flow sensor. During preoxygenation, the operator will ensure the jaw is pulled forward with a two-handed thenar eminence grip. After general anaesthetic induction, the NIV mask will be removed, enabling laryngoscopy vision. No ventilation will be performed during the apnoea. The nasal cannula will be maintained during the laryngoscopic procedure.

Outcomes

Primary outcome measure

Primary outcome variable is the lowest oxygen saturation indicated by SpO2 during the intubation procedure. The intubation procedure lasts from the beginning of the first laryngoscopy (the end of rapid sequence induction) to the confirmation of the orotracheal intubation by capnography after the patient is connected to mechanical ventilation.[17]

Secondary outcome measures

Secondary outcome variables are preoxygenation quality (duration, ability to improve SpO2, proportion of patients in whom it is impossible to obtain a saturation > 90% during preoxygenation), complications related to intubation (severe: severe hypoxemia defined by lowest saturation < 80 %, severe cardiovascular collapse, defined as systolic blood pressure less than 65 mm Hg recorded at least once or less than 90 mm Hg lasting 30 minutes despite 500–1,000 ml of fluid loading (crystalloids solutions) or requiring introduction or increasing doses by more than 30% of vasoactive support, cardiac arrest, death during intubation; moderate: difficult intubation, severe ventricular or supraventricular arrhythmia requiring intervention, oesophageal intubation, agitation, pulmonary aspiration, dental injuries), morbidity in ICU (ICU length of stay, invasive ventilator-free days and mortality rate on day 28).

A previous trial showed that preoxygenation using NIV was more effective at reducing arterial oxyhemoglobin lowest saturation than the usual method.[12] Therefore, the study protocol stresses that NIV must be used as the reference group in the OPTINIV trial, as stated by the unit protocols,[3 5] which are followed for each intubation procedure. Other pre-intubation procedures included in the unit protocols consist of fluid loading if there is no cardiogenic edema, preparation of sedation by the nursing team and presence of two operators. The availability of equipment for management of a difficult airway will be checked. During the procedure, the patient will be ventilated in case of desaturation to less than 80 %. In case of inadequate ventilation and unsuccessful intubation, emergency non-invasive airway ventilation (supraglottic airway) will be used. The difficulty of intubation will be assessed using the MACOCHA score.[2] If a difficult intubation is predicted (MACOCHA score ≥ 3), the use of a malleable stylet and of videolaryngoscopy or combo videolaryngoscopy will be recommended. In cases of abundant secretions even after aspiration, direct laryngoscopy will be preferred rather than videolaryngoscopy. Finally, in cases of intubation failure, an intubating stylet (malleable stylet or long flexible angulated stylet) will be added first, followed successively by the use of videolaryngoscopy if not initially used, an intubation laryngeal mask airway, fiberoscopy and finally the use of rescue percutaneal or surgical airway. The

rapid sequence induction of general anaesthesia for orotracheal intubation under laryngoscopy will be used according to the unit protocol,[5] with a Sellick maneuver,[25] a hypnotic drug (Ketamine 2,5 mg/kg) in the absence of contraindications and a neuromuscular blocker (either Suxamethonium 1 mg/kg in the absence of allergy and other contraindications such as hyperkalliemia, burns, rhabdomyolysis, neuromuscular disease, or Rocuronium 1 mg/kg). A metal blade will be used.[26] Just after intubation (post-intubation period), the tube's position will be checked by capnography, long-term sedation will be initiated as soon as possible (to avoid agitation)[5] and 'protective' mechanical ventilation settings will be used, as defined by the acute respiratory distress syndrome network.[27] At any time, vasopressors will be mandatory in the event of severe hemodynamic collapse.

Participant timeline

The participant timeline is described in Table 1.

Sample size

The primary outcome is the lowest oxygen saturation during intubation procedure. For this study, 2 × 23 patients are needed to detect a 5% difference in the lowest oxygen saturation during intubation procedure, with a standard deviation of 6%, at a two-sided α level of 0.05 and a statistical power of 80%.[4 10 12] To take into account withdrawn consent after randomisation, inclusions not meeting the inclusion criteria or improvement before intubation, 25 patients will be included in each group.

Recruitment

Patients are expected to be included during a one-year inclusion period starting July 2015.

2015: Protocol, approvals from ethics committee, and trial tool development (case report form, randomisation system).

2015 to 2016: Inclusion of patients.

2016: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

A computer-generated randomisation will be used, which will be generated by a statistician who is not involved in determination of patient eligibility or outcome assessment. Randomisation will be accomplished by using opaque sealed envelopes. The randomisation envelopes will contain a card stating the group to which the patient was randomised.

Blinding

The study will be blinded to the observer collecting data (Figure 3). NIV will be performed and nasal cannula positioned in both groups, to allow blinding. The operator performing the intubation will blind the group by placing a large sheet over the oxygen flow meter (Figure 3). In the interventional group (called A. Real HFNC+NIV in the figure 3), the nasal cannula will be connected to the oxygen flow meter via a tube and oxygen set at 60L/min and 100% of FiO2. In the reference group (called B. Fake HFNC+NIV in the figure 3), the tube connected to the nasal cannula positioned on the patient will be hidden under the sheet, without connection to the oxygen flow meter. No flow of oxygen will be administered by the nasal cannula in the reference group. To mimic the noise of HFNC in the reference group, another nasal cannula will be hidden under the sheet and connected to the oxygen flow meter, with a flow also set at 60L/min delivered in the room atmosphere (Figure 3). The blinded observer will be one of the ICU residents, a nurse or a member of the trained local research team.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on case report forms by trained local research coordinators or residents, blinded to the randomised intervention. Patients will receive standard intensive care unit monitoring consisting of electrocardiogram analysis, SpO2, and a noninvasive blood pressure cuff. Prior to orotracheal intubation, the nurse will set the time intervals on the noninvasive blood pressure cuff monitoring and electronic medical record in

the patient's room to run every minute until 15 minutes after successful intubation. Continuously throughout the procedure (from preoxygenation to one hour following intubation) vital parameters will be collected by a software on an external laptop called S5/Collect by General Electric, on the General Electric Carescape monitors.

The following data will be collected and registered before intubation: demographic and epidemiologic data : age, sex, weight, height, date and hour of intubation, on-call procedure, severity scores (Simplified Acute Physiologic Score (SAPS) II at admission, Sequential Organ Failure Assessment (SOFA) score on the day of the procedure), type of admission, reason of ICU admission, indication of intubation, co morbidities. The following parameters will be recorded during the four hours before intubation: nature and number of operators, and their training, arterial pressure and lowest saturation, arterial blood gases with calculated PaO2/FiO2 ratio, delay between the time where the intubation is decided and its realization, presence of vasopressor drugs, prior NIV use, existence of predictive criteria of difficult intubation evaluated by the MACOCHA score.[2]

During preoxygenation, the following data will be recorded: the length of preoxygenation, the vital parameters (oxygen saturation at the beginning and at the end of the preoxygenation, lowest oxygen saturation, lowest and highest arterial pressure and heart rate).

During the intubation procedure, the following parameters will be collected : doses of hypnotic and neuromuscular blocker used, oxygen saturation at the beginning and at the end, lowest oxygen saturation, mild (<90%), moderate (<85%) or severe (<80%) hypoxemia, total duration of the intubation procedure, number of operators, number of attempts, Cormack grade, traction force on the laryngoscope, Sellick maneuver, difficult intubation (more than 2 attempts), modified Intubation Difficulty Scale (IDS score)[28] and occurrence of complications related to intubation.

After the intubation procedure (until one hour after): arterial blood gases with calculated PaO2/FiO2 ratio will be performed at 5-min and 30-min. Complications occurring

will be collected: cardiac arrest, arrhythmias, pneumothorax, arterial hypotension, hypoxemia, agitation, death.

From postoperative day 1 to day 28 will be assessed: morbi-mortality by the length of mechanical ventilation, the length of stay in ICU and the mortality at day 28.

Statistical methods

Statistical analysis

A predefined statistical analysis plan will be followed. The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention to-treat population, including all the randomised patients except patients who withdraw their consent, do not meet the inclusion criteria or improve before intubation. All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, version 9.3; SAS Institute; Cary, NC, USA, and R, version 2.14.1). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described, using n (%) for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables.

Analysis of the primary outcome

Unpaired t test or the Mann–Whitney U test when appropriate will be used for primary outcome analysis.

Analysis of secondary outcomes

The chi-square test (or Fisher's exact test as appropriate) will be used for secondary binary outcomes. Continuous variables will be compared with the use of the unpaired t test or the Mann–Whitney U test when appropriate.

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICU attended formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the type of preoxygenation used.

Auditing

An independent data and safety monitoring board, composed of three experts (Catherine Paugam, Karim Asehnoune and Emmanuel Futier) will monitor the safety of the trial.

ETHICS AND DISSEMINATION

Research ethics approval

The Institutional Review Board of the University Hospital of Montpellier (France) approved the trial. By May 13 2015, the study has been approved by a central ethics committee (Comité de Protection des Personnes Sud-Méditerranée IV, Montpellier, France) with the registration number IDRCB 2015-A00708-41. The OPTINIV study is conducted in accordance with the declaration of Helsinki and was registered on at http://www.clinicaltrials.gov with trial identification number NCT02530957.

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki (Appendix 1). If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of hypoxemia. These patients will be included after written informed consent is provided by next of kin or an emergency procedure (investigator signature) if next of kin is not present. When available, after recovery, patients will be retrospectively asked for written consent to continue the trial.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians,

commissioners and service users. All investigators will have access to the final data set.

Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

Intubation in ICU is associated with severe hypoxemia.[2 4] Optimizing preoxygenation is, therefore, of particular importance before the intubation procedure, especially in hypoxemic patients needing mechanical ventilation for acute respiratory failure. However, although NIV preoxygenation is effective to reduce hypoxemia during intubation procedure,[12] NIV mask has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. Association of HFNC to alveolar recruitment by NIV could be of particular interest both for increasing administration of oxygen during preoxygenation, and to allow apnoeic oxygenation during the apnoea period, time where the hypoxemic patient usually receives no oxygen. This period without oxygenation can last several minutes, especially when the intubation is difficult.

The OPTINIV trial is the first randomised controlled study powered to investigate the effectiveness of combined NIV and HFNC to decrease severe hypoxemia during the intubation procedure in hypoxemic acute respiratory failure patients in ICU.

Apnoeic oxygenation is a physiological phenomenon in which, provided that a patent air passageway exists between the lungs and the exterior, the difference between the alveolar rates of oxygen removal and carbon dioxide excretion generates a negative pressure gradient of up to 20 cmH2O that drives oxygen into the lungs.[18 29 30] The aim of apnoeic oxygenation use throughout the intubation procedure is therefore to reduce severe hypoxemia occurrence during intubation procedure.[31] Previous studies assessed the effect of apnoeic oxygenation, with conflicting results. Apnoeic oxygenation increased the time to severe desaturation during the intubation procedure in acute lung injury in an experimental study in piglets.[32] Miguel-Montanes et al.[16] compared 3 minutes of preoxygenation using a face mask to 60 L/min of HFNC in patients with mild-to-moderate hypoxemia. With the face mask, the median lowest SpO2 during intubation was 94% versus 100% with HFNC. Vourc'h et al[17] found no difference on lowest arterial oxygen during intubation in hypoxemic patients between 60L/min of HFNC and 4-minutes of preoxygenation with a face mask (92% vs 90%,

p= 0.44). Semler et al.[23] performed a randomised trial in a medical ICU, enrolling 150 patients. The administration of 15L/min nasal cannula oxygen in the apnoeic oxygenation group was not associated with significantly increased arterial oxygen saturation (from 92% in the apnoeic oxygenation group to 90% in the usual care group (p= 0.16)). The discrepancies between the results of these 3 studies[16 17 23] could mainly be explained by the oxygen flow used for the apnoeic oxygenation group (from 15 to 60 L/min) and the different studied populations in term of hypoxemia. Moreover, the design of these studies differ from the design of the current study, which allows to specifically study apnoeic oxygenation by HFNC simultaneously combined with NIV preoxygenation.

The primary endpoint of the trial is the lowest oxygen saturation during intubation procedure. The incidence of severe hypoxemia following intubation is particularly high in ICU, reaching up to 50%.[2 4] The ability to anticipate hypoxemia occurrence is of critical importance to prevent the development of subsequent complications. Severe hypoxemia can lead to cardiac arrest, neurologic damage, or multiple organ failure.[2] Moreover, since we collect and report on most complications related to intubation, either severe or moderate, it may still be possible to determine the effects of combined preoxygenation on other complications.

One limitation of the study is that the operator performing intubation can be aware of the group of inclusion. However, the assessor is an independent observer, who does not know the group of inclusion. Some could highlight the risk of gastric air insufflation and aspiration related to positive airway pressure of NIV as a method of preoxygenation. However, as previously reported[12 17 26 33] and in the present study, it will be recommended to never exceed a total insufflation airway pressure (PS+PEEP) of 15 cmH2O which has been shown to be safe to avoid gastric air insufflation.[34-36] Moreover, adding a nasal cannula under the NIV mask may generate leaks during NIV and decrease its efficacy. However, the operator performing intubation holds the mask, which limits the leaks, and the two groups are treated similarly. Finally, given the error of measure associated with SpO2 monitors (usually around 2%) and the error associated with the oxygen blender (around 2%), one could argue

that in fact, difference in SpO2 could be solely due to devices' imprecision. However, given the randomized design of the study, this imprecision should be evenly distributed in each group.

One strength of the study is the blinded assessment (see above, Figure 3). Moreover, the inclusions will be performed around the clock, nights and week-end included as a routine clinical practice.

In conclusion, the OPTINIV trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that adding HFNC in combination with NIV in comparison to NIV alone allows to decrease severe hypoxemia during the intubation procedure of hypoxemic ICU patients requiring mechanical ventilation for acute respiratory failure. The OPTINIV trial will also assess the effects of combined NIV and HFNC for preoxygenation on intubation-related complications.

Trial status

The trial is ongoing and is actively enrolling.

Abbreviations

ICU: Intensive Care Unit; NIV: Noninvasive ventilation; PS : Pressure support; PEEP : Positive end expiratory pressure; HFNC: High-flow nasal cannula oxygen therapy; SpO2: pulse oxymetry; FiO2: fraction inspired in oxygen; PaO2/FiO2: Arterial oxygen tension to inspiratory oxygen fraction ratio; SAPS : Simplified Acute Physiologic Score; SOFA : Sequential Organ Failure Assessment

References

1. Chan AW, Tetzlaff JM, Gotzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
2. De Jong A, Molinari N, Terzi N, *et al.* Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187(8):832-9.
3. De Jong A, Jung B, Jaber S. Intubation in the ICU: we could improve our practice. *Crit Care* 2014;18(2):209.
4. Jaber S, Amraoui J, Lefrant J-Y, *et al.* Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Crit Care Med* 2006;34(9):2355-61.
5. Jaber S, Jung B, Corne P, *et al.* An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive care medicine* 2010;36(2):248-55.
6. Martin LD, Mhyre JM, Shanks AM, *et al.* 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114(1):42-48.
7. Peterson GN, Domino KB, Caplan RA, *et al.* Management of the difficult airway: a closed claims analysis. *Anesthesiology* 2005;103(1):33-39.
8. De Jong A, Futier E, Millot A, *et al.* How to preoxygenate in operative room: Healthy subjects and situations "at risk". *Ann Fr Anesth Reanim* 2014;33(7-8):457-61.
9. De Jong A, Molinari N, Pouzeratte Y, *et al.* Difficult intubation in obese patients: incidence, risk factors, and complications in the operating theatre and in intensive care units. *Br J Anaesth* 2015;114(2):297-306.
10. De Jong A, Clavieras N, Conseil M, *et al.* Implementation of a combo videolaryngoscope for intubation in critically ill patients: a before-after comparative study. *Intensive care medicine* 2013;39(12):2144-52.
11. De Jong A, Molinari N, Conseil M, *et al.* Video laryngoscopy versus direct laryngoscopy for orotracheal intubation in the intensive care unit: a systematic review and meta-analysis. *Intensive care medicine* 2014;40(5):629-39.
12. Baillard C, Fosse J-P, Sebbane M, *et al.* Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med* 2006;174(2):171-77.
13. Jaber S, Michelet P, Chanques G. Role of non-invasive ventilation (NIV) in the perioperative period. *Best practice & research Clinical anaesthesiology* 2010;24(2):253-65.
14. Chanques G, Constantin JM, Sauter M, *et al.* Discomfort associated with underhumidified high-flow oxygen therapy in critically ill patients. *Intensive Care Med* 2009;35(6):996-1003.
15. Chanques G, Jaber S. Unexpected progress of an old intensive care therapy, oxygen: towards more comfort and less mechanical ventilation... *Rev Mal Respir* 2013;30(8):605-8.
16. Miguel-Montanes R, Hajage D, Messika J, *et al.* Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. *Crit Care Med* 2015;43(3):574-83.
17. Vourc'h M, Asfar P, Volteau C, *et al.* High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled clinical trial. *Intensive care medicine* 2015;41(9):1538-48.
18. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. *Anesthesiology* 1959;20:789-98.
19. Patel A, Nouraei SA. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia* 2015;70(3):323-9.

20. Kolettas A, Grosomanidis V, Kolettas V*, et al.* Influence of apnoeic oxygenation in respiratory and circulatory system under general anaesthesia. *Journal of thoracic disease* 2014;6 Suppl 1:S116-45.
21. Futier E, Jaber S. High-flow nasal cannula following extubation: is more oxygen flow useful after surgery? *Intensive care medicine* 2015;41(7):1310-3.
22. Chanques G, Riboulet F, Molinari N*, et al.* Comparison of three high flow oxygen therapy delivery devices: a clinical physiological cross-over study. *Minerva Anestesiol* 2013;79(12):1344-55.
23. Semler M, Janz D, Lentz R*, et al.* Randomized trial of apneic oxygenation during endotracheal intubation of the critically ill. *Am J Respir Crit Care Med* 2015.
24. Jaber S, Chanques G, Jung B. Postoperative noninvasive ventilation. *Anesthesiology* 2010;112(2):453-61.
25. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961;2(7199):404-6.
26. Amour J, Marmion F, Birenbaum A*, et al.* Comparison of plastic single-use and metal reusable laryngoscope blades for orotracheal intubation during rapid sequence induction of anesthesia. *Anesthesiology* 2006;104(1):60-64.
27. Hager DN, Krishnan JA, Hayden DL*, et al.* Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005;172(10):1241-5.
28. Adnet F, Borron SW, Racine SX*, et al.* The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *Anesthesiology* 1997;87(6):1290-97.
29. Bartlett RG, Jr., Brubach HF, Specht H. Demonstration of aventilatory mass flow during ventilation and apnea in man. *J Appl Physiol* 1959;14(1):97-101.
30. Fraioli RL, Sheffer LA, Steffenson JL. Pulmonary and cardiovascular effects of apneic oxygenation in man. *Anesthesiology* 1973;39(6):588-96.
31. De Jong A, Jaber S. Apneic oxygenation for intubation in the critically ill: let's not give up! *Am J Respir Crit Care Med* 2016;In press.
32. Engstrom J, Hedenstierna G, Larsson A. Pharyngeal oxygen administration increases the time to serious desaturation at intubation in acute lung injury: an experimental study. *Crit Care* 2010;14(3):R93.
33. Futier E, Constantin JM, Pelosi P*, et al.* Noninvasive ventilation and alveolar recruitment maneuver improve respiratory function during and after intubation of morbidly obese patients: a randomized controlled study. *Anesthesiology* 2011;114(6):1354-63.
34. Lawes EG, Campbell I, Mercer D. Inflation pressure, gastric insufflation and rapid sequence induction. *Br J Anaesth* 1987;59(3):315-8.
35. Ho-Tai LM, Devitt JH, Noel AG*, et al.* Gas leak and gastric insufflation during controlled ventilation: face mask versus laryngeal mask airway. *Can J Anaesth* 1998;45(3):206-11.
36. Delay JM, Sebbane M, Jung B*, et al.* The effectiveness of noninvasive positive pressure ventilation to enhance preoxygenation in morbidly obese patients: a randomized controlled study. *Anesth Analg* 2008;107(5):1707-13.

Authors' contributions

ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ. NM and ADJ wrote the statistical analysis plan and estimated the sample size. All authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding statement

The study is an investigator-initiated trial. Study promoter is Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Competing interests

Dr. Jaber reports receiving consulting fees from Drager, Hamilton, Maquet and Fisher & Paykel. No potential conflict of interest relevant to this article was reported for other authors.

Table 1. Participant timeline

	Inclusion	Discharge from ICU	Day 28
Informed consent	X		
Eligibility: check inclusion and exclusion criteria	X		
Randomisation	X		
Filling of case report forms	X	X	X
Vital status			X

ICU, Intensive care unit

Figure Legend

Figure 1

Consort diagram of the OPTINIV trial
ABG: Arterial blood gas; NIV : Non invasive ventilation; HFNC : High-flow nasal cannula oxygen therapy; PS : Pressure support; PEEP : Positive end expiratory pressure; FiO2 : Fraction of inspired oxygen.

Figure 2

Study design of the OPTINIV trial
NIV: Noninvasive ventilation; HFNC: High-flow nasal cannula oxygen therapy; PS: Pressure support; PEEP: Positive end expiratory pressure; FiO2: Fraction of inspired oxygen; ICU: Intensive Care Unit.

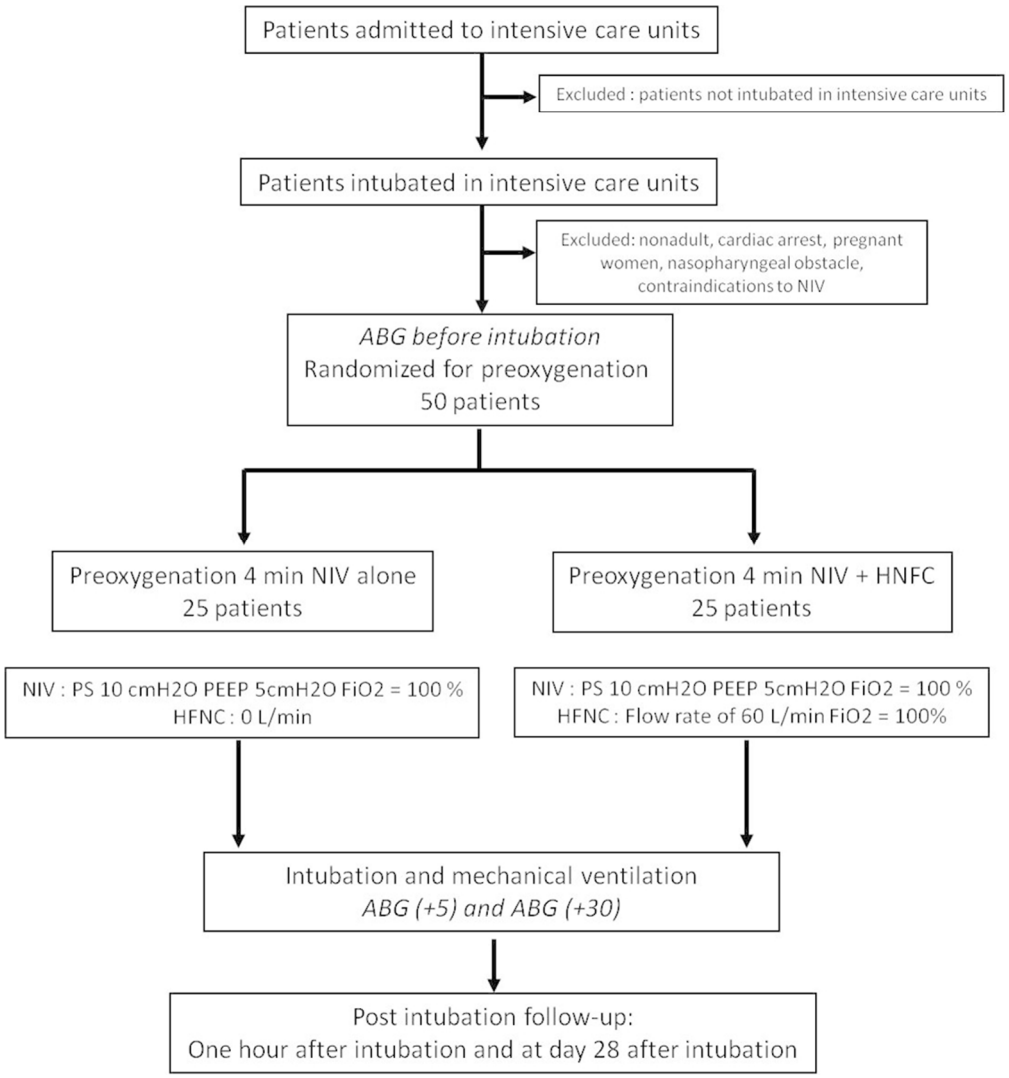
Figure 3

Blinding sequence of the OPTINIV trial
To allow blinding, nasal cannula will be positioned in each group. The operator performing the intubation will blind the group by placing a large sheet over the oxygen flow meter. Both groups will receive VNI.

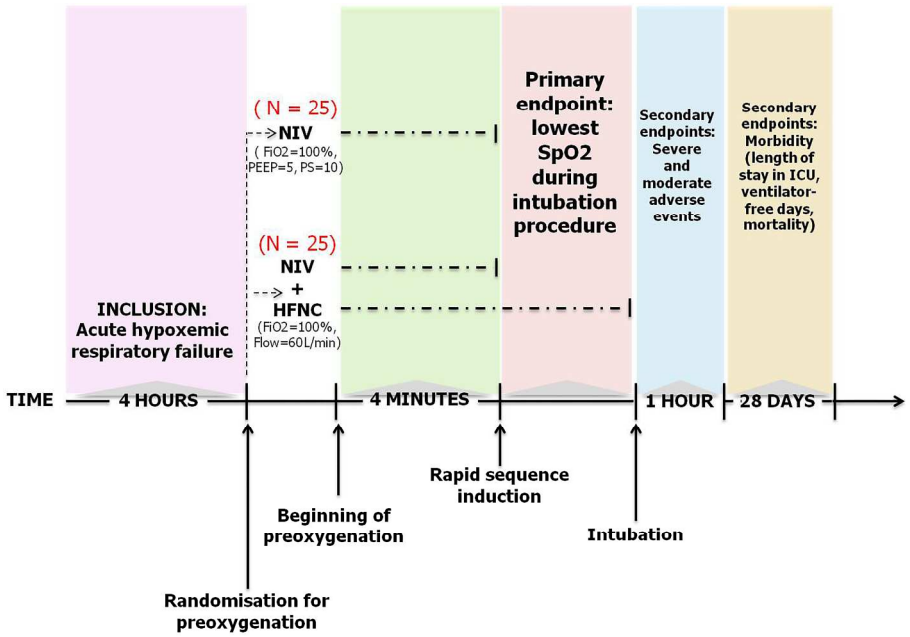
A. Interventional group
In the interventional group (real HFNC+NIV), the nasal cannula will be connected to the oxygen flow meter via a tube and oxygen set at 60L/min and 100% of FiO2 which will be delivered to the patient. The interventional group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV (PS of 10 cmH2O, PEEP of 5cm H2O, FiO2 = 100%) and oxygen HFNC set at 60L/min and 100% of FiO2.

B. Reference group
In the reference group (Fake HFNC+NIV), no oxygen flow will be administered by the nasal cannula to the patient. The tube connected to the nasal cannula positioned on the patient will be hidden under the sheet, without connection to the oxygen flow meter. To mimic the noise of HFNC in the reference group, another nasal cannula will be hidden under the sheet and connected to the oxygen flow meter, with a flow also set at 60L/min.
The reference group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV only (PS of 10 cmH2O, PEEP of 5 cmH2O, FiO2 = 100%) without oxygen HFNC (nasal cannula positioned without any flow).

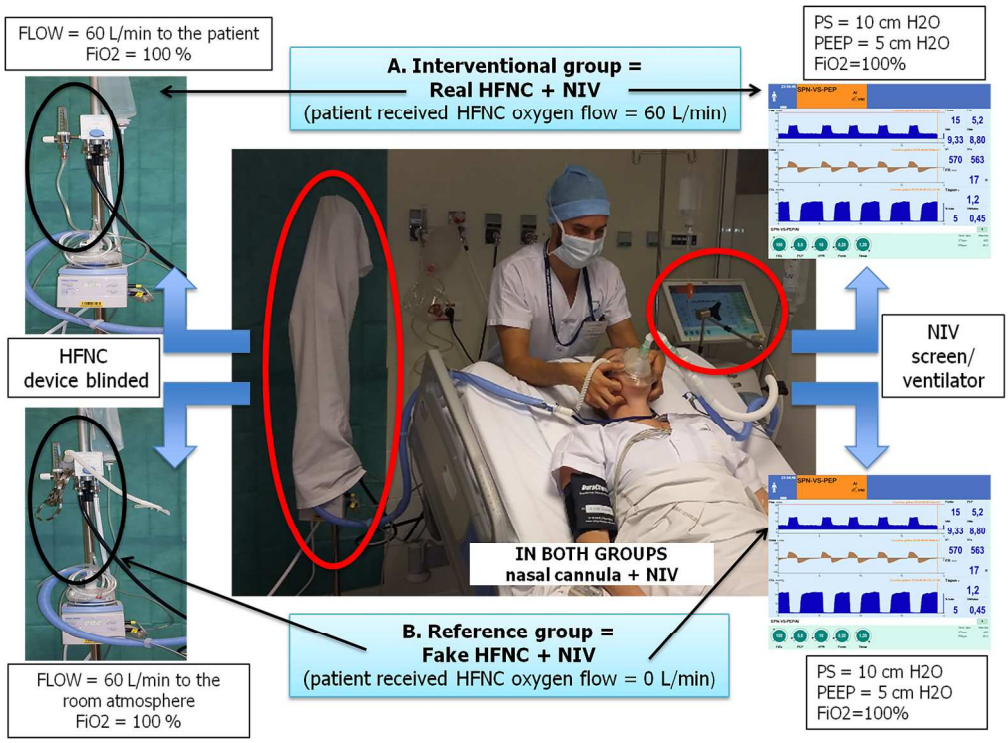
HFNC: High-flow nasal cannula oxygen therapy; FiO2 : Inspired fraction of oxygen; NIV : Noninvasive ventilation; PS : Pressure support; PEEP : Positive end expiratory pressure



92x98mm (300 x 300 DPI)



276x175mm (300 x 300 DPI)



248x182mm (300 x 300 DPI)

Formulaire de consentement patient

Je, soussigné (e)

Nom et Prénom : .....
Adresse : .....

Accepte, par la présente, de participer à la recherche intitulée : **Comparaison de deux méthodes de pré-oxygénation avant intubation oro-trachéale en urgence chez le patient en insuffisance respiratoire aigue hypoxémique en réanimation: Ventilation Non Invasive (VNI) + oxygénothérapie par optiflow® vs VNI seule: une étude randomisée contrôlée** dont le promoteur est le CHRU de Montpellier, coordonné et conduite par le Docteur De Jong au sein de votre établissement.

Ce formulaire a été établi conformément à la loi sur les recherches biomédicales : titre 2 du livre I du code de la santé publique.

J'ai lu ce jour la note d'information réservée au patient, et j'ai bien pris connaissance de l'objectif de l'étude, des bénéfices attendus, des contraintes et des risques prévisibles. De plus les conditions de sa réalisation m'ont été clairement indiquées par le médecin cité plus haut.

Je certifie sur l'honneur être affilié à un régime de Sécurité Sociale.

J'ai bien noté que le présent consentement ne décharge pas le promoteur et l'investigateur de leurs responsabilités et je conserve tous mes droits garantis par la loi.

Ma participation est volontaire. Je connais la possibilité qui m'est réservée à tout moment d'interrompre ma participation sans en fournir la raison et sans que cela ne me porte préjudice, ni que cela porte atteinte aux soins qui continueront à m'être prodigués.

Je m'engage à ne participer à aucun protocole randomisé pendant la durée de l'étude.

J'ai bien noté que j'ai le droit d'être informé(e) des résultats globaux de cette recherche selon les modalités qui ont été précisées dans la note d'information.

J'ai reçu les résultats de l'examen médical préalable qui m'ont été communiqués par l'intermédiaire du médecin de mon choix.

Les données de cette étude resteront strictement confidentielles. Je n'autorise leur consultation que par les personnes qui collaborent à la recherche, désignées par l'investigateur. En application de la loi "Informatique et Liberté" du 6 Janvier 1978, modifiée par les lois n° 94-548 du 1er Juillet 1994, n° 2002-303 du 4 mars 2002, et 2004-801 du 6 août 2004, j'accepte que les données enregistrées à l'occasion de cette étude, y compris les données dites sensibles (origine ethnique, religion, appartenance politique…)[1] puissent faire l'objet d'un traitement par le promoteur ou pour son compte. J'ai bien noté que les droits d'accès (article 39) et de rectification (article 40), que m'ouvrent les textes susvisés, pourront s'exercer à tout moment auprès du Dr De Jong, et que les données me concernant pourront m'être communiquées directement ou par l'intermédiaire d'un médecin de mon choix.

J'ai bien noté que cette étude a reçu l'autorisation de l'ANSM (Agence Nationale du Médicament) et l'avis favorable du CPP Sud-méditerranée 4 (Comité de Protection des Personnes).

J'ai bénéficié d'un temps de réflexion suffisant entre ces informations et le présent consentement.

J'ai lu et reçu un exemplaire de ce formulaire et j'accepte de participer au présent protocole.

Partie à compléter par le patient

Fait à ....., le …….

Nom et Prénom du patient

Signature du patient

Partie à compléter par le médecin-investigateur

J'ai oralement expliqué l'étude au patient en termes appropriés et compréhensibles. Je pense avoir informé complètement le patient sur la nature de cette étude et sur ses avantages et risques potentiels.

Fait à ....., le …….

Nom et Prénom du médecin investigateur

Signature de l'investigateur

<u>Promoteur :</u>
Le Centre Hospitalier Universitaire de Montpellier
CHU de Montpellier
191, Avenue du Doyen Gaston Giraud
34295 MONTPELLIER CEDEX 5

<u>Investigateur coordonnateur :</u>
Docteur Audrey DE JONG
Téléphone : 04.67.33.72.71

Formulaire de consentement de participation à une recherche biomédicale *en situation d'urgence* pour le représentant (personne de confiance ou à défaut membre de la famille ou proche du patient présent) d'une personne adulte hors d'état d'exprimer son consentement (article L1122-1-2 du CSP).

Je soussigné(e),

Nom ……

Prénom ……

Adresse ……

accepte librement et volontairement en qualité de proche ou de parent, personne de confiance* (rayer la mention inutile) que

M^me^, M^elle^, M (rayer les mentions inutiles)
Nom, prénom……
né(e) le ……

participe à la recherche biomédicale intitulée **"Comparaison de deux méthodes de pré-oxygénation avant intubation oro-trachéale en urgence chez le patient en insuffisance respiratoire aigue hypoxémique en réanimation: Ventilation Non Invasive (VNI) + oxygénothérapie par optiflow® vs VNI seule: une étude randomisée contrôlée"** dont le Centre Hospitalier Universitaire de Montpellier est le promoteur (UF 9543) et qui m'a été proposée par le Professeur / Docteur (nom, prénom,)…… médecin investigateur dans cette recherche.

Etant entendu que :

- J'ai bien compris dans la note d'information qui m'a été remise, les objectifs, les bénéfices et les risques de la recherche pour la participation de mon proche à cette étude.
- J'ai bénéficié d'un temps de réflexion suffisant entre ces informations et le présent consentement,
- Le médecin qui m'a informé et a répondu à toutes mes questions m'a précisé que j'étais libre d'accepter ou de refuser que mon proche participe à cette recherche.
- Mon proche pourra avoir communication par le médecin au cours ou à l'issue de la recherche des informations concernant sa santé.
- J'ai bien noté que pour que mon proche puisse participer à cette recherche, il doit être affilié(e) ou bénéficier d'un régime de sécurité sociale.
- J'ai bien noté que la participation de mon proche à la recherche est volontaire. Je suis parfaitement conscient(e) que je peux retirer à tout moment mon consentement pour la participation de mon proche à la recherche, cela quelles que soient mes raisons et sans supporter aucune responsabilité, mais je m'engage dans ce cas à en informer le médecin. Le fait que mon proche ne participe plus à cette étude ne portera pas atteinte à ses relations avec le médecin qui me proposera pour mon proche, si je le souhaite et si j'en ai besoin, une autre prise en charge.
- S'il le souhaite, à son terme, mon proche sera informé(e) par le médecin des résultats globaux de cette recherche.
- Mon consentement ne décharge en rien le médecin et le promoteur de l'ensemble de leurs responsabilités, mon proche conservant tous ses droits garantis par la loi.
- J'ai bien noté que cette étude a reçu l'autorisation de l'ANSM et l'avis favorable du CPP Sud méditerranée IV (Comité de Protection des Personnes).

Ce formulaire a été établi conformément à la Loi sur les Recherches Biomédicales : Titre 2 du Livre I du Code de La Santé Publique.

J'ai lu et reçu un exemplaire signé de ce document et j'accepte que mon proche participe à cette recherche biomédicale.

Les données de cette étude resteront strictement confidentielles. Je n'autorise leur consultation que par les personnes qui collaborent à la recherche, désignées par l'investigateur. En application de la loi "Informatique et Liberté" du 6 Janvier 1978, modifiée par les lois n° 94-548 du 1er Juillet 1994, n° 2002-303 du 4 mars 2002, et 2004-801 du 6 août 2004, j'accepte que les données de mon proche enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement par le promoteur. J'ai bien noté que les droits d'accès (article 39) et de rectification (article 40), que m'ouvrent les textes susvisés, pourront s'exercer à tout moment auprès du Docteur Audrey DE JONG, et que les données concernant mon proche pourront m'être communiquées directement ou par l'intermédiaire d'un médecin de mon choix.

Lien avec l'intéressé(e) : ……..
J'accepte que mon proche participe à cette recherche.
Fait à …….. le ……
Signature du proche:

Signature du médecin qui atteste avoir pleinement expliqué à la personne signataire le but, les modalités ainsi que les risques potentiels de cette recherche.
Date ……
Signature :

* **La personne de confiance** doit avoir été désignée au préalable par écrit par le patient (art. L.1111-6 CSP)

Promoteur :
Le Centre Hospitalier Universitaire de Montpellier
CHU de Montpellier
191, Avenue du Doyen Gaston Giraud
34295 MONTPELLIER CEDEX 5

Investigateur coordonnateur :
Dr Audrey DE JONG
Téléphone : 04.67.33.72.71

Formulaire de consentement patient
Pour la poursuite de l'étude et l'utilisation des données collectées dans le cadre d'une recherche biomédicale

Je soussigné(e),

Nom ……
Prénom ……
Adresse ……

accepte librement et volontairement que le médecin cité ci-après utilise les données collectées dans le cadre de ma participation

à la recherche biomédicale intitulée **"*Comparaison de deux méthodes de pré-oxygénation avant intubation oro-trachéale en urgence chez le patient en insuffisance respiratoire aigüe hypoxémique en réanimation: Ventilation Non Invasive (VNI) + oxygénothérapie par optiflow® vs VNI seule: une étude randomisée contrôlée*"** dont le Centre Hospitalier Universitaire de Montpellier est le promoteur et l'investigateur principal le Docteur Audrey DR JONG, Département d'anesthésie - réanimation B - Hôpital Saint - Eloi, 34295 Montpellier Cedex 5.

Etant entendu que :

- J'ai bien compris dans la note d'information qui m'a été remise, les objectifs, les bénéfices et les risques de la recherche pour ma participation à cette étude.
- J'ai bénéficié d'un temps de réflexion suffisant entre ces informations et le présent consentement,
- Le médecin qui m'a informé et a répondu à toutes mes questions m'a précisé que ma participation est libre et que mon droit de retrait de cette recherche peut s'exercer à tout moment.
- Je pourrai avoir communication par le médecin au cours ou à l'issue de la recherche des informations qu'il détient concernant ma santé.
- J'ai bien compris dans la note d'information qui m'a été remise que pour pouvoir participer à cette recherche, je dois être affilié(e) ou bénéficier d'un régime de sécurité sociale.
- J'ai bien noté que ma participation est volontaire. Je suis parfaitement conscient(e) que je peux retirer à tout moment mon consentement à ma participation à cette recherche, cela quelles que soient mes raisons et sans supporter aucune responsabilité, mais je m'engage dans ce cas à en informer le médecin. Le fait de ne plus participer à cette recherche ne portera pas atteinte à mes relations avec ce médecin.
- Si je le souhaite, à son terme, je serai informé(e) par le médecin des résultats globaux de cette recherche.
- Mon consentement ne décharge en rien le médecin et le promoteur de l'ensemble de leurs responsabilités et je conserve tous mes droits garantis par la loi.
- J'ai bien noté que cette étude a reçu l'autorisation de l'ANSM et l'avis favorable du CPP Sud méditerranée IV.

Ce formulaire a été établi conformément à la Loi sur les Recherches Biomédicales : Titre 2 du Livre I du Code de La Santé Publique.

J'ai lu et reçu un exemplaire signé de ce document et j'accepte de participer à cette recherche biomédicale.

Ce document est à réaliser en 3 exemplaires originaux, dont le premier doit être gardé pendant 15 ans par l'investigateur, un autre remis à la personne donnant son consentement et le troisième transmis au promoteur.

Les données de cette étude resteront strictement confidentielles. Je n'autorise leur consultation que par les personnes qui collaborent à la recherche, désignées par l'investigateur. En application de la loi "Informatique et Liberté" du 6 Janvier 1978, modifiée par les lois n° 94-548 du 1er Juillet 1994, n° 2002-303 du 4 mars 2002, et 2004-801 du 6 août 2004, j'accepte que les données enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement par le promoteur ou pour son compte. J'ai bien noté que les droits d'accès (article 39) et de rectification (article 40), que m'ouvrent les textes susvisés, pourront s'exercer à tout moment auprès du Docteur Audrey DE JONG, et que les données me concernant pourront m'être communiquées directement ou par l'intermédiaire d'un médecin de mon choix.

J'accepte de participer à cette recherche.
Fait à…….…….. le ……

Signature du patient :

Signature du médecin qui atteste avoir pleinement expliqué à la personne signataire le but, les modalités ainsi que les risques potentiels de cette recherche.
Date …….

Signature du médecin :

Promoteur :
Le Centre Hospitalier Universitaire de Montpellier
CHU de Montpellier
191, Avenue du Doyen Gaston Giraud
34295 MONTPELLIER CEDEX 5

Investigateur coordonnateur :
Docteur Audrey DE JONG
Téléphone : 04.67.33.72.71

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **PAGE 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **PAGE 14**
	2b	All items from the World Health Organization Trial Registration Data Set **PAGE 6 and 14**
Protocol version	3	Date and version identifier **PAGE 14**
Funding	4	Sources and types of financial, material, and other support **PAGE 20**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **PAGE 1**
	5b	Name and contact information for the trial sponsor **PAGE 14**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **PAGE 14**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **PAGE 13**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **PAGE 4**
	6b	Explanation for choice of comparators **PAGE 4**
Objectives	7	Specific objectives or hypotheses **PAGE 5**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **PAGE 6**

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **PAGE 6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **PAGE 6**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **PAGE 7**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **PAGE 7**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **PAGE 7**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **PAGE 7**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **PAGE 7**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **PAGE 9 and 20**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **PAGE 9**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **PAGE 9**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **PAGE 10**

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are Assigned **PAGE 10**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **PAGE 10**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and How **PAGE 10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **PAGE 10**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **PAGE 10**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **PAGE 10**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **PAGE 10 and 11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **PAGE 12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **PAGE 12**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **PAGE 12**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **PAGE 13**

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **PAGE 13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **PAGE 13**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the Sponsor **PAGE 13**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **PAGE 14**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **PAGE 14**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **PAGE 14**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **PAGE 14**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **PAGE 14**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **PAGE 14**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for Investigators **PAGE 14**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **NOT APPLICABLE**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **PAGE 14 and 15**
	31b	Authorship eligibility guidelines and any intended use of professional Writers **PAGE 21**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **PAGE 15**

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **APPENDIX 1**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **NOT APPLICABLE**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons " Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

A new method of preoxygenation for orotracheal intubation in hypoxemic acute respiratory failure patients in intensive care unit, noninvasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-011298.R2
Article Type:	Protocol
Date Submitted by the Author:	27-May-2016
Complete List of Authors:	Jaber, S.; Saint-Eloi Hospital, University Teaching Hospital of Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B); INSERM U1046 MOLINARI, Nicolas; University of Montpellier Lapeyronie Hospital, Department of Statistics, UMR 729 MISTEA DE JONG, Audrey; Saint-Eloi Hospital, University Teaching Hospital of Montpellier, Department of Anaesthesiology and Critical Care Medicine B (DAR B); INSERM U1046
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia, Emergency medicine, Medical management
Keywords:	Adult intensive & critical care < ANAESTHETICS, Adult thoracic medicine < THORACIC MEDICINE, Respiratory physiology < THORACIC MEDICINE

Study protocol

A new method of preoxygenation for orotracheal intubation in hypoxemic acute respiratory failure patients in intensive care unit, noninvasive ventilation combined with apnoeic oxygenation by high flow nasal oxygen: the randomised OPTINIV study protocol

Samir Jaber,[1,2] Nicolas Molinari,[3] Audrey De Jong[1,2]

[1]Department of Anaesthesiology and Critical Care Medicine B (DAR B), Saint-Eloi Hospital, University Teaching Hospital of Montpellier, 80 avenue Augustin Fliche, 34295 Montpellier, France

[2] INSERM U1046 Montpellier, France

[3] Department of Statistics, University of Montpellier Lapeyronie Hospital, UMR 729 MISTEA, Montpellier, France

Correspondence: Pr Samir JABER, Intensive Care Unit & Anaesthesiology Department, University of Montpellier Saint-Eloi Hospital. Montpellier, France; 80 avenue Augustin Fliche. 34295 Montpellier Cedex 5, France
Tel: 00. 33. 467. 337. 271; Fax: 00. 33. 467.337. 448; E-mail: s-jaber@chu-montpellier.fr

Abstract

Introduction: Tracheal intubation in the intensive care unit (ICU) is associated with severe life-threatening complications including severe hypoxemia. Preoxygenation before intubation has been recommended in order to decrease such complications. Non invasive ventilation (NIV)-assisted preoxygenation allows increased oxygen saturation during intubation procedure, by applying a positive-end expiratory pressure (PEEP) to prevent alveolar derecruitment. However, the NIV-mask has to be taken off after preoxygenation to allow the passage of the tube through the mouth. The hypoxemic patient does not receive oxygen during this period, at risk of major hypoxemia. High-flow nasal cannula oxygen (HFNC) has a potential of apnoeic oxygenation during the apnoea period following the preoxygenation with NIV. Whether application of HFNC combined with NIV is more effective at reducing oxygen desaturation during the intubation procedure compared to NIV alone for preoxygenation in hypoxemic ICU patients with acute respiratory failure remains to be established.

Methods and analysis: The HFNC combined to NIV for decreasing oxygen desaturation during the intubation procedure in ICU hypoxemic patients (OPTINIV) trial is an investigator-initiated monocenter randomised controlled two-arm trial with assessor-blinded outcome assessment. The OPTINIV trial randomises 50 hypoxemic patients requiring orotracheal intubation for acute respiratory failure to receive NIV (Pressure support=10, PEEP=5, inspired fraction of oxygen (FiO2)=100%) combined with HFNC (Flow=60L/min, FiO2=100%, interventional group) or NIV alone (reference group) for preoxygenation. The primary outcome is lowest oxygen saturation during the intubation procedure. Secondary outcomes are intubation-related complications, quality of preoxygenation and ICU mortality.

Ethics and dissemination: The study project has been approved by the appropriate ethics committee (CPP Sud-Méditerranée). Informed consent is required. If combined application of HFNC and NIV for preoxygenation of ICU hypoxemic patients proves superior to NIV preoxygenation, its use will become standard practice, thereby decreasing hypoxemia during intubation procedure and potentially complications related to intubation.

Trial registration: ClinicalTrials.gov Identifier: NCT02530957.

Strengths and limitations of the study: Strengths of the study are the blinded assessment. and the inclusions performed around the clock, nights and week-end included as a routine clinical practice. Limitations of the study are that the operator performing intubation can be aware of the group of inclusion. However, the assessor is an independent observer, who

does not know the group of inclusion. Some could highlight the risk of gastric air insufflation and aspiration related to positive airway pressure of NIV as a method of preoxygenation. However, as previously reported and in the present study, it will be recommended to never exceed a total insufflation airway pressure (PS+PEEP) of 15 cmH2O which has been shown to be safe to avoid gastric air insufflation.

Keywords: Preoxygenation, non invasive ventilation, oxygen therapy, complications related to intubation, acute respiratory failure, intensive care unit, critical care

INTRODUCTION

Background and rationale

This manuscript was written in accordance with the SPIRIT guidelines.[1]

Patients admitted to Intensive Care Units (ICU) often require respiratory support. Hypoxemia and cardiovascular collapse are the initial and most serious life-threatening complications associated with difficult airway access, both during emergency intubation in the critically ill[2-6] and in planned intubations (e. g., scheduled surgery or invasive procedures).[7 8] ICU intubation conditions are worse than intubation conditions in operative rooms.[4 9] A non planned and urgent intubation procedure, severity of patient disease and ergonomic issues explain the morbidity associated with intubation in ICU. To prevent and limit the incidence of severe hypoxemia following intubation and its complications, several pre-oxygenation techniques and intubation algorithms have been developed ,[3 5 10 11] and specific risk factors for difficult intubation in ICU have been identified, constituting the MACOCHA score (Mallampati score III or IV, obstructive sleep Apnoea syndrome, reduced mobility of Cervical spine, limited mouth Opening < 3 cm, Coma, severe Hypoxemia (<80%) and non Anaesthesiologist status).[2]

Noninvasive ventilation (NIV) for preoxygenation of patients with hypoxemic acute respiratory failure is associated with less hypoxemia than preoxygenation with nonrebreather bag-valve mask during intubation procedure.[12] Indeed, associating Pressure Support (PS) with Positive end expiratory pressure (PEEP) limits alveolar collapse and atelectasis formation, responsible for hypoventilation and low perfusion ventilation ratio.[8 13] Incidence of severe hypoxemia defined by a pulse oxymetry (SpO2) of less than 80% can be decreased by applying NIV preoxygenation, a method which is now used by many teams for preoxygenation of patients with hypoxemic acute respiratory failure.[2]

However, although NIV can be safely applied for preoxygenation before intubation procedure, NIV mask has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. Furthermore, positioning the orotracheal tube into the trachea may take time, from a few seconds to several minutes in case of difficult

intubation. The hypoxemic patient does not receive oxygen during this period, which participates in the risk of severe hypoxemia during intubation.

High-flow nasal cannula oxygen therapy (HFNC), which delivers high flow heated and humidified oxygen and air via nasal prongs at a prescribed fraction of inspired oxygen (FiO2) and a maximum flow of 60 L/min,[14-17] can be continued during the passage of orotracheal tube through the mouth. Apnoeic oxygenation maintains blood oxygenation for a significant period of time in breathless conditions.[18] Recent studies suggest that HFNC could allow apnoeic oxygenation,[16 19 20] and as a consequence could be interestingly used to continue blood oxygenation during the apnoea period of intubation, especially when the NIV mask is removed. Furthermore, previous studies have shown that HFNC oxygen therapy generates a flow-dependent positive airway pressure and improves oxygenation by increasing end-expiratory lung volume,[21] thus suggesting possible associated alveolar recruitment . However, the patients' mouth must be closed to observe this effect ,[22] suggesting that NIV could be more efficient than HFNC to prevent alveolar derecruitment.

Using HFNC combined with NIV may have potential advantages over conventional NIV alone for preoxygenation before intubation in hypoxemic ICU patients. Some studies have assessed the preoxygenation effect of HFNC compared to facial mask or other devices, with conflicting results.[16 17 23] However, the technique of preoxygenation associating NIV and HFNC, respectively combining the concepts of prevention of alveolar derecruitment and of apnoeic oxygenation, has never been assessed and benefit remains to be established.

Objectives

Primary objective. To determine whether application of HFNC combined with NIV is more effective at reducing oxygen desaturation during intubation procedure over NIV alone for preoxygenation in ICU patients needing mechanical ventilation for hypoxemic acute respiratory failure.

Secondary objectives. To determine whether in comparison to NIV alone, application of HFNC combined to NIV could provide a better preoxygenation quality, less complications related to intubation, decrease in ICU morbidity and mortality day-28 rate.

The OPTINIV study aims to compare the effects of preoxygenation with a combination of NIV and HFNC delivered together compared with NIV alone on lowest oxygen saturation during intubation procedure and complications related to intubation of ICU hypoxemic patients needing mechanical ventilation for hypoxemic acute respiratory failure.

The hypothesis is that preoxygenation combining NIV and HFNC compared to NIV alone could prevent desaturation during the intubation procedure.

Trial design

The HFNC (Optiflow®, Fisher & Paykel Healthcare, Auckland, NZ) combined to NIV for decreasing oxygen desaturation during the intubation procedure in ICU hypoxemic patients (OPTINIV) trial is an investigator initiated single center randomised controlled two-arm trial.

CONSORT diagram

Figure 1 shows the CONSORT diagram of the OPTINIV trial.

METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

Study setting

The OPTINIV study is taking place in a mixed medical and surgical 16-bed ICU, in France.

Eligibility criteria

Inclusion criteria

Patients must be present in the ICU and require mechanical ventilation through an orotracheal tube. Hypoxemic acute respiratory failure is defined as a respiratory rate higher than 30 per minute and a FiO2 requirement of 50% or more to obtain at least 90% oxygen saturation, and an estimated arterial oxygen tension to fraction inspired in oxygen (PaO2/FiO2 ratio) below 300 mmHg, in the 4 hours before inclusion.[17]

Exclusion criteria

Patients fulfilling one or more of the following criteria will not be included:

age <18 years, pregnant or breastfeeding woman, protected person, intubation in case of cardio circulatory arrest, nasopharyngeal obstacle contraindicating the use of HFNC and usual contraindications to NIV.[24]

Interventions

Patients eligible for inclusion will be randomly assigned to the interventional group or to the reference group (Figure 2). The interventional group consists in applying preoxygenation at 30 degrees of head-up inclination with NIV (PS of 10 cmH2O, PEEP of 5cm H2O, FiO2 = 100%, inspiratory flow trigger at 0,3L/min, expiratory trigger at 25%, maximal inspiratory time at 1.5 s) and HFNC (humidified oxygen flow of 60L/min, FiO2 = 100%, Figure 3A.). We will use an ICU ventilator with NIV software (Evita V500 or XL, Drager Lubeck). The reference group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV only (same parameters as in the interventional group) without HFNC (nasal cannula positioned without any flow, Figure 3B.). The ventilator circuit will be connected to a standard soft style manual resuscitator face mask, with a capnograph inserted between face mask and flow sensor. During preoxygenation, the operator will ensure the jaw is pulled forward with a two-handed thenar eminence grip. After general anaesthetic induction, the NIV mask will be removed, enabling laryngoscopy vision. No ventilation will be performed during the apnoea. The nasal cannula will be maintained during the laryngoscopic procedure.

Outcomes

Primary outcome measure

Primary outcome variable is the lowest oxygen saturation indicated by SpO2 during the intubation procedure. The intubation procedure lasts from the beginning of the first laryngoscopy (the end of rapid sequence induction) to the confirmation of the orotracheal intubation by capnography after the patient is connected to mechanical ventilation.[17]

Secondary outcome measures

Secondary outcome variables are preoxygenation quality (duration, ability to improve SpO2, proportion of patients in whom it is impossible to obtain a saturation > 90% during preoxygenation), complications related to intubation (severe: severe hypoxemia defined by lowest saturation < 80 %, severe cardiovascular collapse, defined as systolic blood pressure less than 65 mm Hg recorded at least once or less than 90 mm Hg lasting 30 minutes despite 500–1,000 ml of fluid loading (crystalloids solutions) or requiring introduction or increasing doses by more than 30% of vasoactive support, cardiac arrest, death during intubation; moderate: difficult intubation, severe ventricular or supraventricular arrhythmia requiring intervention, oesophageal intubation, agitation, pulmonary aspiration, dental injuries), morbidity in ICU (ICU length of stay, invasive ventilator-free days and mortality rate on day 28).

A previous trial showed that preoxygenation using NIV was more effective at reducing arterial oxyhemoglobin lowest saturation than the usual method.[12] Therefore, the study protocol stresses that NIV must be used as the reference group in the OPTINIV trial, as stated by the unit protocols,[3 5] which are followed for each intubation procedure. Other pre-intubation procedures included in the unit protocols consist of fluid loading if there is no cardiogenic edema, preparation of sedation by the nursing team and presence of two operators. The availability of equipment for management of a difficult airway will be checked. During the procedure, the patient will be ventilated in case of desaturation to less than 80 %. In case of inadequate ventilation and unsuccessful intubation, emergency non-invasive airway ventilation (supraglottic airway) will be used. The difficulty of intubation will be assessed using the MACOCHA score.[2] If a difficult intubation is predicted (MACOCHA score ≥ 3), the use of a malleable stylet and of videolaryngoscopy or combo videolaryngoscopy will be recommended. In cases of abundant secretions even after aspiration, direct laryngoscopy will be preferred rather than videolaryngoscopy. Finally, in cases of intubation failure, an intubating stylet (malleable stylet or long flexible angulated stylet) will be added first, followed successively by the use of videolaryngoscopy if not initially used, an intubation laryngeal mask airway, fiberoscopy and finally the use of rescue percutaneal or surgical airway. The

rapid sequence induction of general anaesthesia for orotracheal intubation under laryngoscopy will be used according to the unit protocol,[5] with a Sellick maneuver,[25] a hypnotic drug (Ketamine 2,5 mg/kg) in the absence of contraindications and a neuromuscular blocker (either Suxamethonium 1 mg/kg in the absence of allergy and other contraindications such as hyperkalliemia, burns, rhabdomyolysis, neuromuscular disease, or Rocuronium 1 mg/kg). A metal blade will be used.[26] Just after intubation (post-intubation period), the tube's position will be checked by capnography, long-term sedation will be initiated as soon as possible (to avoid agitation)[5] and 'protective' mechanical ventilation settings will be used, as defined by the acute respiratory distress syndrome network.[27] At any time, vasopressors will be mandatory in the event of severe hemodynamic collapse.

Participant timeline

The participant timeline is described in Table 1.

Sample size

The primary outcome is the lowest oxygen saturation during intubation procedure. For this study, 2 × 23 patients are needed to detect a 5% difference in the lowest oxygen saturation during intubation procedure, with a standard deviation of 6%, at a two-sided α level of 0.05 and a statistical power of 80%. [5 10 12] To take into account withdrawn consent after randomisation, inclusions not meeting the inclusion criteria or improvement before intubation, 25 patients will be included in each group.

Recruitment

Patients are expected to be included during a one-year inclusion period starting July 2015.

2015: Protocol, approvals from ethics committee, and trial tool development (case report form, randomisation system).

2015 to 2016: Inclusion of patients.

2016: Cleaning and closure of the database. Data analyses, writing of the manuscript and submission for publication.

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation and sequence generation

A computer-generated randomisation will be used, which will be generated by a statistician who is not involved in determination of patient eligibility or outcome assessment. Randomisation will be accomplished by using opaque sealed envelopes. The randomisation envelopes will contain a card stating the group to which the patient was randomised.

Blinding

The study will be blinded to the observer collecting data (Figure 3). NIV will be performed and nasal cannula positioned in both groups, to allow blinding. The operator performing the intubation will blind the group by placing a large sheet over the oxygen flow meter (Figure 3). In the interventional group (called A. Real HFNC+NIV in the figure 3), the nasal cannula will be connected to the oxygen flow meter via a tube and oxygen set at 60L/min and 100% of FiO2. In the reference group (called B. Fake HFNC+NIV in the figure 3), the tube connected to the nasal cannula positioned on the patient will be hidden under the sheet, without connection to the oxygen flow meter. No flow of oxygen will be administered by the nasal cannula in the reference group. To mimic the noise of HFNC in the reference group, another nasal cannula will be hidden under the sheet and connected to the oxygen flow meter, with a flow also set at 60L/min delivered in the room atmosphere (Figure 3). The blinded observer will be one of the ICU residents, a nurse or a member of the trained local research team.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection and management

Data will be collected and recorded on case report forms by trained local research coordinators or residents, blinded to the randomised intervention. Patients will receive standard intensive care unit monitoring consisting of electrocardiogram analysis, SpO2, and a noninvasive blood pressure cuff. Prior to orotracheal intubation, the nurse will set the time intervals on the noninvasive blood pressure cuff monitoring and electronic medical record in

the patient's room to run every minute until 15 minutes after successful intubation. Continuously throughout the procedure (from preoxygenation to one hour following intubation) vital parameters will be collected by a software on an external laptop called S5/Collect by General Electric, on the General Electric Carescape monitors.

The following data will be collected and registered before intubation: demographic and epidemiologic data : age, sex, weight, height, date and hour of intubation, on-call procedure, severity scores (Simplified Acute Physiologic Score (SAPS) II at admission, Sequential Organ Failure Assessment (SOFA) score on the day of the procedure), type of admission, reason of ICU admission, indication of intubation, co morbidities. The following parameters will be recorded during the four hours before intubation: nature and number of operators, and their training, arterial pressure and lowest saturation, arterial blood gases with calculated PaO2/FiO2 ratio, delay between the time where the intubation is decided and its realization, presence of vasopressor drugs, prior NIV use, existence of predictive criteria of difficult intubation evaluated by the MACOCHA score.[2]

During preoxygenation, the following data will be recorded: the length of preoxygenation, the vital parameters (oxygen saturation at the beginning and at the end of the preoxygenation, lowest oxygen saturation, lowest and highest arterial pressure and heart rate).

During the intubation procedure, the following parameters will be collected : doses of hypnotic and neuromuscular blocker used, oxygen saturation at the beginning and at the end, lowest oxygen saturation, mild (<90%), moderate (<85%) or severe (<80%) hypoxemia, total duration of the intubation procedure, number of operators, number of attempts, Cormack grade, traction force on the laryngoscope, Sellick maneuver, difficult intubation (more than 2 attempts), modified Intubation Difficulty Scale (IDS score)[28] and occurrence of complications related to intubation.

After the intubation procedure (until one hour after): arterial blood gases with calculated PaO2/FiO2 ratio will be performed at 5-min and 30-min. Complications occurring

will be collected: cardiac arrest, arrhythmias, pneumothorax, arterial hypotension, hypoxemia, agitation, death.

From postoperative day 1 to day 28 will be assessed: morbi-mortality by the length of mechanical ventilation, the length of stay in ICU and the mortality at day 28.

Statistical methods

Statistical analysis

A predefined statistical analysis plan will be followed. The statistical analysis will incorporate all the elements required by the CONSORT statement for non-pharmacological interventions. Statistical analysis will be performed in an intention to-treat population, including all the randomised patients except patients who withdraw their consent, do not meet the inclusion criteria or improve before intubation. All analyses will be conducted by the medical statistical department of the Montpellier University Hospital using statistical software (SAS, version 9.3; SAS Institute; Cary, NC, USA, and R, version 2.14.1). A two-sided p value of less than 0.05 will be considered to indicate statistical significance.

Description of the patient groups at baseline

The baseline features of the overall population and of each group will be described, using n (%) for categorical variables and the minimum, maximum, mean, SD and quartiles for quantitative variables.

Analysis of the primary outcome

Unpaired t test or the Mann–Whitney U test when appropriate will be used for primary outcome analysis.

Analysis of secondary outcomes

The chi-square test (or Fisher's exact test as appropriate) will be used for secondary binary outcomes. Continuous variables will be compared with the use of the unpaired t test or the Mann–Whitney U test when appropriate.

METHODS: MONITORING

Data monitoring

Before the start of patient recruitment, all physicians and other healthcare workers in the ICU attended formal training sessions on the study protocol and data collection.

The physicians and a clinical research nurse and/or clinical research assistant are in charge of daily patient screening and inclusion, ensuring compliance with the study protocol and collecting the study data, with blinded assessment.

Harms

The trial may be temporarily stopped for an individual patient, at the discretion of the attending physician, in case of major serious adverse events suspected to be associated with the type of preoxygenation used.

Auditing

An independent data and safety monitoring board, composed of three experts (Catherine Paugam, Karim Asehnoune and Emmanuel Futier) will monitor the safety of the trial.

ETHICS AND DISSEMINATION

Research ethics approval

The Institutional Review Board of the University Hospital of Montpellier (France) approved the trial. By May 13 2015, the study has been approved by a central ethics committee (Comité de Protection des Personnes Sud-Méditerranée IV, Montpellier, France) with the registration number IDRCB 2015-A00708-41. The OPTINIV study is conducted in accordance with the declaration of Helsinki and was registered on at http://www.clinicaltrials.gov with trial identification number NCT02530957.

Consent or assent

Three methods of consent will be used, as required by the institutional review board in accordance with the 2013 Declaration of Helsinki (Appendix 1). If possible, the patient will be included after written informed consent. However, the patient often cannot understand information given because of hypoxemia. These patients will be included after written informed consent is provided by next of kin or an emergency procedure (investigator signature) if next of kin is not present. When available, after recovery, patients will be retrospectively asked for written consent to continue the trial.

Confidentiality

Data will be handled according to French law. All original records will be archived at trial sites for 15 years. The clean database file will be anonymized and kept for 15 years.

Declaration of interest

The study is an investigator-initiated trial. Study promotion is performed by Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Dissemination policy

Findings will be published in peer-reviewed journals and presented at local, national and international meetings and conferences to publicise and explain the research to clinicians,

commissioners and service users. All investigators will have access to the final data set.

Participant-level data sets will be made accessible on a controlled access basis.

DISCUSSION

Intubation in ICU is associated with severe hypoxemia.[2 4] Optimizing preoxygenation is, therefore, of particular importance before the intubation procedure, especially in hypoxemic patients needing mechanical ventilation for acute respiratory failure. However, although NIV preoxygenation is effective to reduce hypoxemia during intubation procedure,[12] NIV mask has to be taken off after preoxygenation in order to allow the passage of the orotracheal tube through the mouth. Association of HFNC to alveolar recruitment by NIV could be of particular interest both for increasing administration of oxygen during preoxygenation, and to allow apnoeic oxygenation during the apnoea period, time where the hypoxemic patient usually receives no oxygen. This period without oxygenation can last several minutes, especially when the intubation is difficult.

The OPTINIV trial is the first randomised controlled study powered to investigate the effectiveness of combined NIV and HFNC to decrease severe hypoxemia during the intubation procedure in hypoxemic acute respiratory failure patients in ICU.

Apnoeic oxygenation is a physiological phenomenon in which, provided that a patent air passageway exists between the lungs and the exterior, the difference between the alveolar rates of oxygen removal and carbon dioxide excretion generates a negative pressure gradient of up to 20 cmH2O that drives oxygen into the lungs.[18 29 30] The aim of apnoeic oxygenation use throughout the intubation procedure is therefore to reduce severe hypoxemia occurrence during intubation procedure.[31] Previous studies assessed the effect of apnoeic oxygenation, with conflicting results. Apnoeic oxygenation increased the time to severe desaturation during the intubation procedure in acute lung injury in an experimental study in piglets.[32] Miguel-Montanes et al.[16] compared 3 minutes of preoxygenation using a face mask to 60 L/min of HFNC in patients with mild-to-moderate hypoxemia. With the face mask, the median lowest SpO2 during intubation was 94% versus 100% with HFNC. Vourc'h et al[17] found no difference on lowest arterial oxygen during intubation in hypoxemic patients between 60L/min of HFNC and 4-minutes of preoxygenation with a face mask (92% vs 90%,

p= 0.44). Semler et al.[23] performed a randomised trial in a medical ICU, enrolling 150 patients. The administration of 15L/min nasal cannula oxygen in the apnoeic oxygenation group was not associated with significantly increased arterial oxygen saturation (from 92% in the apnoeic oxygenation group to 90% in the usual care group (p= 0.16)). The discrepancies between the results of these 3 studies[16 17 23] could mainly be explained by the oxygen flow used for the apnoeic oxygenation group (from 15 to 60 L/min) and the different studied populations in term of hypoxemia. Moreover, the design of these studies differ from the design of the current study, which allows to specifically study apnoeic oxygenation by HFNC simultaneously combined with NIV preoxygenation. However, the current study will not conclude on the superiority or not of NIV over HFNC alone, and therefore on the best means to ensure preoxygenation.

The primary endpoint of the trial is the lowest oxygen saturation during intubation procedure. The incidence of severe hypoxemia following intubation is particularly high in ICU, reaching up to 50%.[2 4] The ability to anticipate hypoxemia occurrence is of critical importance to prevent the development of subsequent complications. Severe hypoxemia can lead to cardiac arrest, neurologic damage, or multiple organ failure.[2] Moreover, since we collect and report on most complications related to intubation, either severe or moderate, it may still be possible to determine the effects of combined preoxygenation on other complications.

One limitation of the study is that the operator performing intubation can be aware of the group of inclusion. However, the assessor is an independent observer, who does not know the group of inclusion. Some could highlight the risk of gastric air insufflation and aspiration related to positive airway pressure of NIV as a method of preoxygenation. However, as previously reported[12 17 26 33] and in the present study, it will be recommended to never exceed a total insufflation airway pressure (PS+PEEP) of 15 cmH2O which has been shown to be safe to avoid gastric air insufflation.[34-36] Moreover, adding a nasal cannula under the NIV mask may generate leaks during NIV and decrease its efficacy. However, the operator performing intubation holds the mask, which limits the leaks, and the two groups are

treated similarly. Finally, given the error of measure associated with SpO2 monitors (usually around 2%) and the error associated with the oxygen blender (around 2%), one could argue that in fact, difference in SpO2 could be solely due to devices' imprecision. However, given the randomized design of the study, this imprecision should be evenly distributed in each group.

One strength of the study is the blinded assessment (see above, Figure 3). Moreover, the inclusions will be performed around the clock, nights and week-end included as a routine clinical practice.

In conclusion, the OPTINIV trial is an investigator initiated pragmatic randomised controlled trial powered to test the hypothesis that adding HFNC in combination with NIV in comparison to NIV alone allows to decrease severe hypoxemia during the intubation procedure of hypoxemic ICU patients requiring mechanical ventilation for acute respiratory failure. The OPTINIV trial will also assess the effects of combined NIV and HFNC for preoxygenation on intubation-related complications.

Trial status

The trial is ongoing and is actively enrolling.

Abbreviations

ICU: Intensive Care Unit; NIV: Noninvasive ventilation; PS : Pressure support; PEEP : Positive end expiratory pressure; HFNC: High-flow nasal cannula oxygen therapy; SpO2: pulse oxymetry; FiO2: fraction inspired in oxygen; PaO2/FiO2: Arterial oxygen tension to inspiratory oxygen fraction ratio; SAPS : Simplified Acute Physiologic Score; SOFA : Sequential Organ Failure Assessment

References

1. Chan AW, Tetzlaff JM, Gotzsche PC, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
2. De Jong A, Molinari N, Terzi N, *et al.* Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187(8):832-9.
3. De Jong A, Jung B, Jaber S. Intubation in the ICU: we could improve our practice. *Crit Care* 2014;18(2):209.
4. Jaber S, Amraoui J, Lefrant J-Y, *et al.* Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Crit Care Med* 2006;34(9):2355-61.
5. Jaber S, Jung B, Corne P, *et al.* An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive care medicine* 2010;36(2):248-55.
6. Martin LD, Mhyre JM, Shanks AM, *et al.* 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114(1):42-48.
7. Peterson GN, Domino KB, Caplan RA, *et al.* Management of the difficult airway: a closed claims analysis. *Anesthesiology* 2005;103(1):33-39.
8. De Jong A, Futier E, Millot A, *et al.* How to preoxygenate in operative room: Healthy subjects and situations "at risk". *Ann Fr Anesth Reanim* 2014;33(7-8):457-61.
9. De Jong A, Molinari N, Pouzeratte Y, *et al.* Difficult intubation in obese patients: incidence, risk factors, and complications in the operating theatre and in intensive care units. *Br J Anaesth* 2015;114(2):297-306.
10. De Jong A, Clavieras N, Conseil M, *et al.* Implementation of a combo videolaryngoscope for intubation in critically ill patients: a before-after comparative study. *Intensive care medicine* 2013;39(12):2144-52.
11. De Jong A, Molinari N, Conseil M, *et al.* Video laryngoscopy versus direct laryngoscopy for orotracheal intubation in the intensive care unit: a systematic review and meta-analysis. *Intensive care medicine* 2014;40(5):629-39.
12. Baillard C, Fosse J-P, Sebbane M, *et al.* Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med* 2006;174(2):171-77.
13. Jaber S, Michelet P, Chanques G. Role of non-invasive ventilation (NIV) in the perioperative period. *Best practice & research Clinical anaesthesiology* 2010;24(2):253-65.

14. Chanques G, Constantin JM, Sauter M*, et al.* Discomfort associated with underhumidified high-flow oxygen therapy in critically ill patients. *Intensive Care Med* 2009;35(6):996-1003.
15. Chanques G, Jaber S. Unexpected progress of an old intensive care therapy, oxygen: towards more comfort and less mechanical ventilation... *Rev Mal Respir* 2013;30(8):605-8.
16. Miguel-Montanes R, Hajage D, Messika J*, et al.* Use of high-flow nasal cannula oxygen therapy to prevent desaturation during tracheal intubation of intensive care patients with mild-to-moderate hypoxemia. *Crit Care Med* 2015;43(3):574-83.
17. Vourc'h M, Asfar P, Volteau C*, et al.* High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled clinical trial. *Intensive care medicine* 2015;41(9):1538-48.
18. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. *Anesthesiology* 1959;20:789-98.
19. Patel A, Nouraei SA. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia* 2015;70(3):323-9.
20. Kolettas A, Grosomanidis V, Kolettas V*, et al.* Influence of apnoeic oxygenation in respiratory and circulatory system under general anaesthesia. *Journal of thoracic disease* 2014;6 Suppl 1:S116-45.
21. Futier E, Jaber S. High-flow nasal cannula following extubation: is more oxygen flow useful after surgery? *Intensive care medicine* 2015;41(7):1310-3.
22. Chanques G, Riboulet F, Molinari N*, et al.* Comparison of three high flow oxygen therapy delivery devices: a clinical physiological cross-over study. *Minerva Anestesiol* 2013;79(12):1344-55.
23. Semler M, Janz D, Lentz R*, et al.* Randomized trial of apneic oxygenation during endotracheal intubation of the critically ill. *Am J Respir Crit Care Med* 2015.
24. Jaber S, Chanques G, Jung B. Postoperative noninvasive ventilation. *Anesthesiology* 2010;112(2):453-61.
25. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet* 1961;2(7199):404-6.
26. Amour J, Marmion F, Birenbaum A*, et al.* Comparison of plastic single-use and metal reusable laryngoscope blades for orotracheal intubation during rapid sequence induction of anesthesia. *Anesthesiology* 2006;104(1):60-64.
27. Hager DN, Krishnan JA, Hayden DL*, et al.* Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. *Am J Respir Crit Care Med* 2005;172(10):1241-5.

28. Adnet F, Borron SW, Racine SX*, et al.* The intubation difficulty scale (IDS): proposal and evaluation of a new score characterizing the complexity of endotracheal intubation. *Anesthesiology* 1997;87(6):1290-97.
29. Bartlett RG, Jr., Brubach HF, Specht H. Demonstration of aventilatory mass flow during ventilation and apnea in man. *J Appl Physiol* 1959;14(1):97-101.
30. Fraioli RL, Sheffer LA, Steffenson JL. Pulmonary and cardiovascular effects of apneic oxygenation in man. *Anesthesiology* 1973;39(6):588-96.
31. De Jong A, Jaber S. Apneic oxygenation for intubation in the critically ill: let's not give up! *Am J Respir Crit Care Med* 2016;In press.
32. Engstrom J, Hedenstierna G, Larsson A. Pharyngeal oxygen administration increases the time to serious desaturation at intubation in acute lung injury: an experimental study. *Crit Care* 2010;14(3):R93.
33. Futier E, Constantin JM, Pelosi P*, et al.* Noninvasive ventilation and alveolar recruitment maneuver improve respiratory function during and after intubation of morbidly obese patients: a randomized controlled study. *Anesthesiology* 2011;114(6):1354-63.
34. Lawes EG, Campbell I, Mercer D. Inflation pressure, gastric insufflation and rapid sequence induction. *Br J Anaesth* 1987;59(3):315-8.
35. Ho-Tai LM, Devitt JH, Noel AG*, et al.* Gas leak and gastric insufflation during controlled ventilation: face mask versus laryngeal mask airway. *Can J Anaesth* 1998;45(3):206-11.
36. Delay JM, Sebbane M, Jung B*, et al.* The effectiveness of noninvasive positive pressure ventilation to enhance preoxygenation in morbidly obese patients: a randomized controlled study. *Anesth Analg* 2008;107(5):1707-13.

Authors' contributions

ADJ drafted the manuscript together with SJ. SJ designed the study together with ADJ. NM and ADJ wrote the statistical analysis plan and estimated the sample size. All authors revised the manuscript for important intellectual content and read and approved the final version of the manuscript.

Funding statement

The study is an investigator-initiated trial. Study promoter is Montpellier University Hospital, Montpellier, France. There is no industry support or involvement in the trial.

Competing interests

Dr. Jaber reports receiving consulting fees from Drager, Hamilton, Maquet and Fisher & Paykel. No potential conflict of interest relevant to this article was reported for other authors.

Table 1. Participant timeline

	Inclusion	Discharge from ICU	Day 28
Informed consent	X		
Eligibility: check inclusion and exclusion criteria	X		
Randomisation	X		
Filling of case report forms	X	X	X
Vital status			X

ICU, Intensive care unit

Figure Legend

Figure 1

Consort diagram of the OPTINIV trial
ABG: Arterial blood gas; NIV : Non invasive ventilation; HFNC : High-flow nasal cannula oxygen therapy; PS : Pressure support; PEEP : Positive end expiratory pressure; FiO2 : Fraction of inspired oxygen.

Figure 2

Study design of the OPTINIV trial
NIV: Noninvasive ventilation; HFNC: High-flow nasal cannula oxygen therapy; PS: Pressure support; PEEP: Positive end expiratory pressure; FiO2: Fraction of inspired oxygen; ICU: Intensive Care Unit.

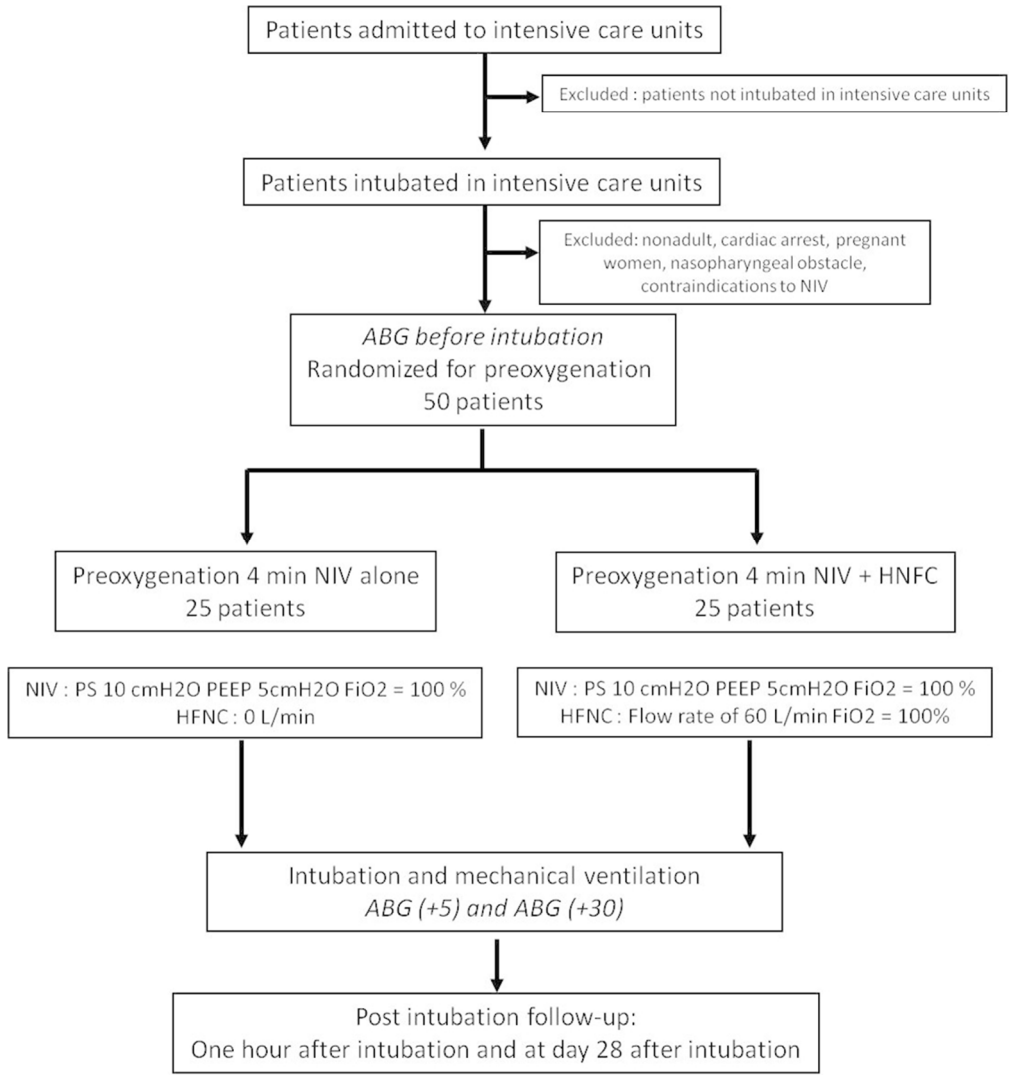
Figure 3

Blinding sequence of the OPTINIV trial
To allow blinding, nasal cannula will be positioned in each group. The operator performing the intubation will blind the group by placing a large sheet over the oxygen flow meter. Both groups will receive VNI.

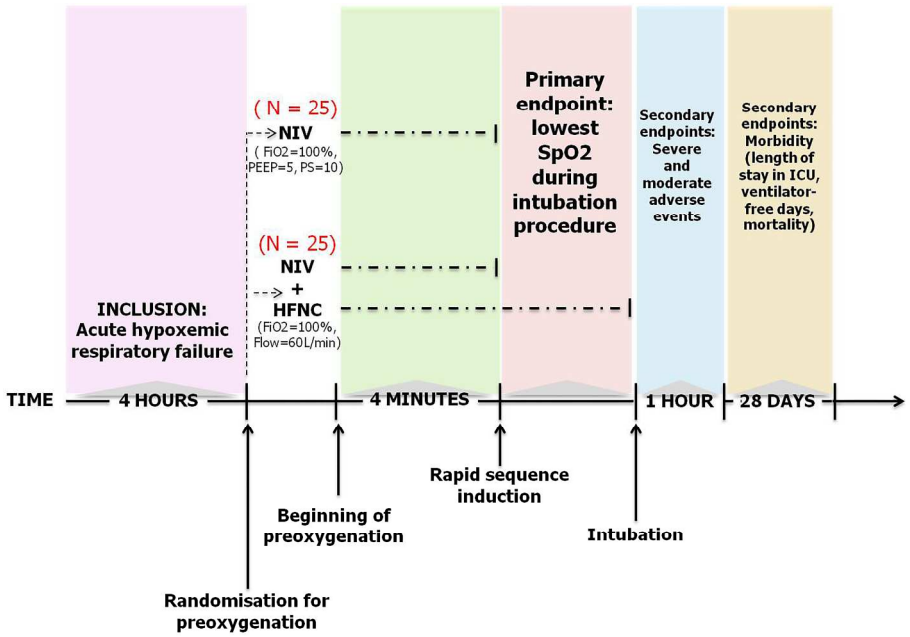
A. Interventional group
In the interventional group (real HFNC+NIV), the nasal cannula will be connected to the oxygen flow meter via a tube and oxygen set at 60L/min and 100% of FiO2 which will be delivered to the patient. The interventional group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV (PS of 10 cmH2O, PEEP of 5cm H2O, FiO2 = 100%) and oxygen HFNC set at 60L/min and 100% of FiO2.

B. Reference group
In the reference group (Fake HFNC+NIV), no oxygen flow will be administered by the nasal cannula to the patient. The tube connected to the nasal cannula positioned on the patient will be hidden under the sheet, without connection to the oxygen flow meter. To mimic the noise of HFNC in the reference group, another nasal cannula will be hidden under the sheet and connected to the oxygen flow meter, with a flow also set at 60L/min.
The reference group consists in applying a preoxygenation at 30 degrees of head-up inclination with NIV only (PS of 10 cmH2O, PEEP of 5 cmH2O, FiO2 = 100%) without oxygen HFNC (nasal cannula positioned without any flow).

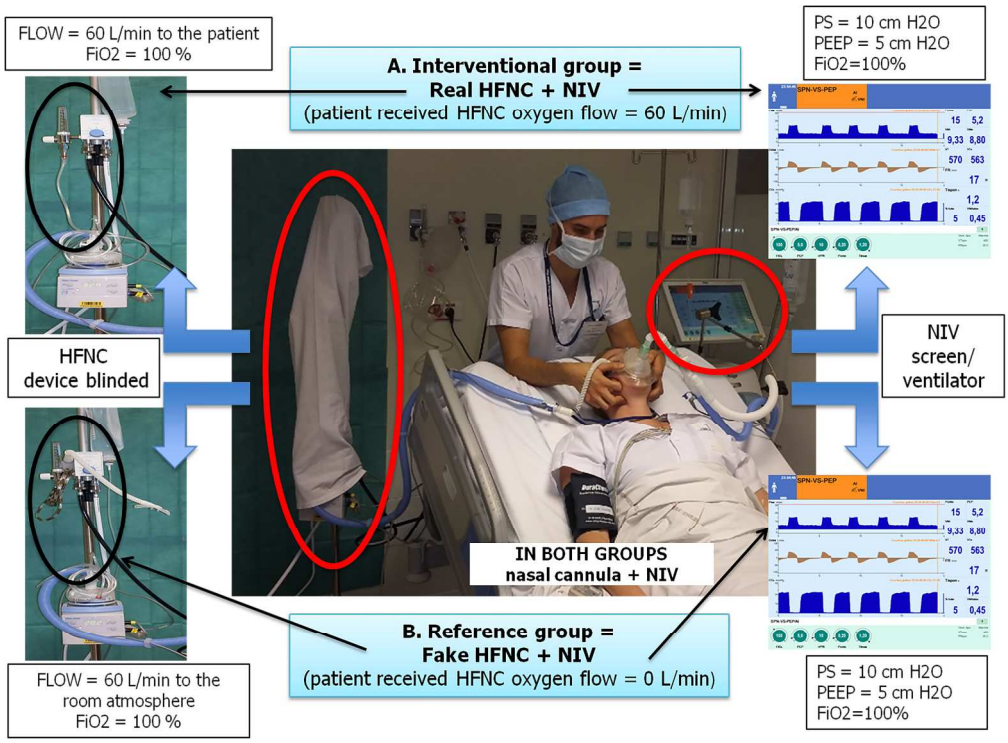
HFNC: High-flow nasal cannula oxygen therapy; FiO2 : Inspired fraction of oxygen; NIV : Noninvasive ventilation; PS : Pressure support; PEEP : Positive end expiratory pressure



92x98mm (300 x 300 DPI)



276x175mm (300 x 300 DPI)



248x182mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **PAGE 1**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **PAGE 14**
	2b	All items from the World Health Organization Trial Registration Data Set **PAGE 6 and 14**
Protocol version	3	Date and version identifier **PAGE 14**
Funding	4	Sources and types of financial, material, and other support **PAGE 20**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **PAGE 1**
	5b	Name and contact information for the trial sponsor **PAGE 14**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities **PAGE 14**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) **PAGE 13**
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention **PAGE 4**
	6b	Explanation for choice of comparators **PAGE 4**
Objectives	7	Specific objectives or hypotheses **PAGE 5**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) **PAGE 6**

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained **PAGE 6**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) **PAGE 6**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **PAGE 7**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) **PAGE 7**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **PAGE 7**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **PAGE 7**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended **PAGE 7**
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) **PAGE 9 and 20**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations **PAGE 9**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **PAGE 9**

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions **PAGE 10**

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are Assigned **PAGE 10**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **PAGE 10**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and How **PAGE 10**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **PAGE 10**
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol **PAGE 10**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols **PAGE 10**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol **PAGE 10 and 11**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol **PAGE 12**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **PAGE 12**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) **PAGE 12**
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed **PAGE 13**

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial **PAGE 13**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct **PAGE 13**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the Sponsor **PAGE 13**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **PAGE 14**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) **PAGE 14**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **PAGE 14**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **PAGE 14**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial **PAGE 14**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **PAGE 14**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for Investigators **PAGE 14**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation **NOT APPLICABLE**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions **PAGE 14 and 15**
	31b	Authorship eligibility guidelines and any intended use of professional Writers **PAGE 21**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **PAGE 15**

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **APPENDIX 1**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable **NOT APPLICABLE**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons " Attribution-NonCommercial-NoDerivs 3.0 Unported" license.