Non-invasive ventilation versus high-flow nasal cannula oxygen therapy with apnoeic oxygenation for preoxygenation before intubation of patients with acute hypoxaemic respiratory failure: a randomised, multicentre, open-label trial

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Summary

Background Non-invasive ventilation has never been compared with high-flow oxygen to determine whether it reduces the risk of severe hypoxaemia during intubation. We aimed to determine if preoxygenation with non-invasive ventilation was more efficient than high-flow oxygen in reducing the risk of severe hypoxaemia during intubation.

Methods The FLORALI-2 multicentre, open-label trial was done in 28 intensive care units in France. Adult patients undergoing tracheal intubation for acute hypoxaemic respiratory failure (a partial pressure of arterial oxygen [PaO_2] to fraction of inspired oxygen [FiO_2] ratio of ≤300 mm Hg) were randomly assigned (1:1; block size, four participants) to non-invasive ventilation or high-flow oxygen during preoxygenation, with stratification by PaO_2/FiO_2 ratio (≤200 mm Hg *vs* >200 mm Hg). Key exclusion criteria were intubation for cardiac arrest, altered consciousness (defined as a Glasgow coma score of less than eight points), other contraindications to non-invasive ventilation (recent laryngeal, oesophageal, or gastric surgery, and substantial facial fractures), pulse oximetry not available, pregnant or breastfeeding women, and refusal to participate. The primary outcome was the occurrence of severe hypoxaemia (pulse oximetry <80%) during the procedure, assessed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT02668458.

Findings Between April 15, 2016, and Jan 8, 2017, 2079 patients were intubated in the 28 participating units, and 322 were enrolled. We excluded five patients with no recorded data, two who withdrew consent or were under legal protection, one who was not intubated, and one who had a cardiac arrest. Of the 313 patients included in the intention-to-treat analysis, 142 were assigned to non-invasive ventilation and 171 to high-flow oxygen therapy. Severe hypoxaemia occurred in 33 (23%) of 142 patients after preoxygenation with non-invasive ventilation and 47 (27%) of 171 with high-flow oxygen (absolute difference −4·2%, 95% CI −13·7 to 5·5; p=0·39). In the 242 patients with moderate-to-severe hypoxaemia (PaO_2/FiO_2 ≤200 mm Hg), severe hypoxaemia occurred less frequently after preoxygenation with non-invasive ventilation than with high-flow oxygen (28 [24%] of 117 patients *vs* 44 [35%] of 125; adjusted odds ratio 0·56, 0·32 to 0·99, p=0·0459). Serious adverse events did not differ between treatment groups, with the most common immediate complications being systolic arterial hypotension (70 [49%] patients in the non-invasive ventilation group *vs* 86 [50%] patients in the high-flow oxygen group) and chest infiltrate on x-ray (28 [20%] *vs* 33 [19%]), and the most common late complications being death at day 28 (53 [37%] *vs* 58 [34%]) and ventilator-associated pneumonia during ICU stay (31 [22%] *vs* 35 [20%]).

Interpretation In patients with acute hypoxaemic respiratory failure, preoxygenation with non-invasive ventilation or high-flow oxygen therapy did not change the risk of severe hypoxaemia. Future research should explore the effect of preoxygenation method in patients with moderate-to-severe hypoxaemia at baseline.

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Introduction

Tracheal intubation is one of the most common procedures done in intensive care units (ICUs).[1] Unlike the operating room, intubation procedures in ICUs have a high risk of life-threatening complications, including severe hypoxaemia, neurological or cardiac ischaemia,

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Research in context

Evidence before this study

We searched PubMed for papers published between Jan 1, 2000, and Oct 1, 2018, using the following search terms: "preoxygenation" OR "preoxygenation" AND "apnoeic oxygenation" AND "non-invasive ventilation". Our search yielded one small randomised control study reporting improved efficacy of non-invasive ventilation in preventing severe hypoxaemia before intubation when compared with standard oxygen using valve-bag mask in patients with acute hypoxaemic respiratory failure. Another study showed a decreased incidence of severe hypoxaemia with high-flow oxygen therapy compared with standard oxygen in a prospective before–after study. However these results were not confirmed in the three randomised controlled trials carried out so far. It, therefore, raises the question of whether non-invasive ventilation, compared with high-flow oxygen therapy, could better prevent severe hypoxaemia during the intubation of patients with hypoxaemic respiratory failure.

Added value of this study

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

Implications of all the available evidence

The findings of the FLORALI-2 trial should be explored as an option for preoxygenation before the intubation of patients with severe hypoxaemic respiratory failure. This subgroup of patients represents more than three-quarters of patients with acute hypoxaemic respiratory failure. On the basis of these results and previous studies, preoxygenation with valve-bag facemasks should be replaced by high-flow nasal cannula oxygen therapy or non-invasive ventilation in ICUs before the intubation of patients with acute mild hypoxaemic respiratory failure. However, further studies are needed in a larger population to investigate whether non-invasive ventilation should be used for all patients regardless of their level of hypoxaemia.

and cardiovascular collapse.[2,3] Severe hypoxaemia occurs in 20–25% of cases, especially in hypoxaemic patients intubated for acute respiratory failure.[2–4] Cardiac arrest, which is the ultimate catastrophic complication, occurs in 2–3% of intubation procedures in ICUs, and is strongly associated with hypoxaemia or absence of preoxygenation before intubation.[5,6] Optimisation of preoxygenation might help to secure the procedure by mitigating the risks of severe hypoxaemia and subsequent complications.

Non-invasive ventilation and high-flow nasal cannula oxygen therapy (high-flow oxygen) are two oxygenation devices largely used in ICUs that provide a higher fraction of inspired oxygen (FiO_2) than does standard oxygen.[7–10] High-flow oxygen enables delivery of continuous high gas flow up to 70 L/min via nasal prongs, resulting in a high FiO_2 (> 0·9) similar to that of a valve-bag mask with reservoir.[7,11] Another theoretical advantage of high-flow oxygen might be the maintenance of oxygenation during the apnoeic phase of intubation after anaesthetic induction, thereby avoiding hypoxaemia; whereas non-invasive ventilation is removed at this phase. High-flow oxygen has also shown a decreased incidence of severe hypoxaemia during intubation compared with standard oxygen in a prospective before–after study.[12] However, these encouraging results were not confirmed in various randomised controlled trials[13–15] done to date. Only one randomised controlled study[16] of a small sample of patients with acute hypoxaemic respiratory failure has shown better efficacy of non-invasive ventilation in preventing severe hypoxaemia, compared with standard oxygen using valve-bag mask. Another study[17] showed a higher rate of severe hypoxaemia with standard oxygen than with non-invasive ventilation in patients previously treated with non-invasive ventilation.

We did a prospective, multicentre, randomised, controlled trial involving patients admitted to an ICU with acute hypoxaemic respiratory failure and undergoing tracheal intubation. We aimed to determine whether non-invasive ventilation could be associated with a lower rate of severe hypoxaemia during the procedure than high-flow oxygen therapy.

Methods

Study design and participants

The FLORALI-2 trial was a non-blinded, multicentre, open-label, parallel-group randomised, controlled trial. Consecutive patients from 28 ICUs in France were randomly assigned to receive either non-invasive ventilation or high-flow oxygen therapy during pre-oxygenation. Eligible patients were older than 18 years, admitted to the ICU, required intubation, and had acute hypoxaemic respiratory failure according to the following criteria: a respiratory rate greater than 25 breaths per min or signs of respiratory distress, and a partial pressure of arterial oxygen (PaO_2) to FiO_2 ratio equal to or below 300 mm Hg, regardless of oxygenation strategy.

To calculate the PaO_2/FiO_2 ratio, we measured FiO_2 under non-invasive-ventilation or high-flow oxygen and estimated FiO_2 under standard oxygen as follows: $FiO_2 = 0{\cdot}21 + \text{oxygen flow rate} \times 0{\cdot}03$.[10]

Key exclusion criteria were intubation for cardiac arrest, altered consciousness (defined as a Glasgow coma score less than eight points), other contraindications to non-invasive ventilation (recent laryngeal, oesophageal, or gastric surgery, and substantial facial fractures), pulse oximetry not available, pregnant or breastfeeding women, and refusal to participate.

The study protocol was approved for all centres by the ethics committee at Poitiers University Hospital. According to French law and the decision of the ethics committee, no safety committee was required because the interventions used in the study were strategies of preoxygenation that are typically used in clinical practice. Written informed consent was obtained from all patients or next of kin before inclusion in the study. The trial was overseen by a steering committee that presented information regarding the progression and monitoring of the study at Réseau Européen de Recherche en Ventilation Artificielle Network meetings to all the investigators or research assistants (or both) of the participating centres every 4 months. The steering committee made decisions, endorsed the actions of the clinical research team, and worked with the public funder (University Hospital of Poitiers). Members of the steering committee were not independent and were also members of the scientist committee, who designed the study. Members checked all relevant publications on the field of the study to ensure consistency in continuing the study. However, they had no access to the data collected or the database until it was locked after the monitoring of centres.

The protocol is available in the appendix. Research assistants regularly monitored all centres on-site to check adherence to the protocol and accuracy of the data recorded in accordance with the Good Clinical Practice Guidelines. An investigator at each centre was responsible for enrolling patients in the study, ensuring adherence to the protocol, and completing the electronic case report form.

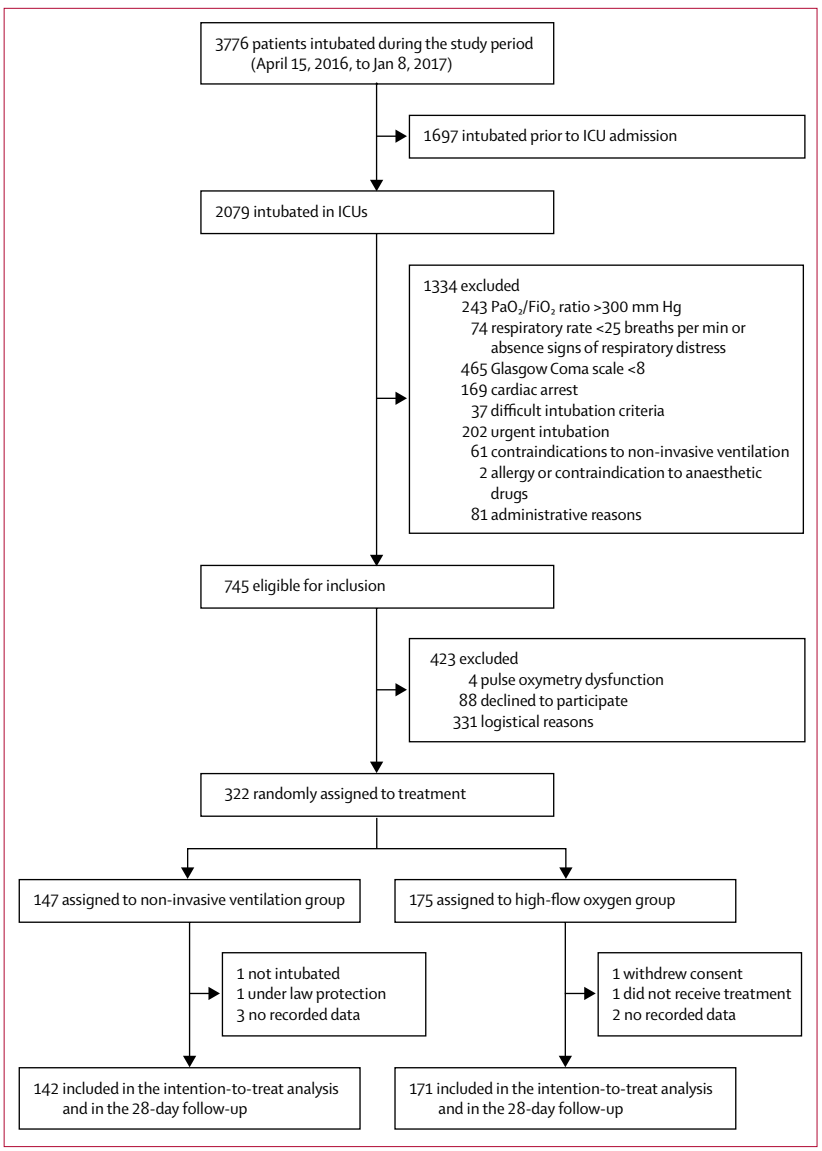

Figure 1: **Trial profile**

Randomisation and masking

Randomisation was computer-generated in permuted blocks of four participants (unknown to investigators), with stratification according to the centre and PaO_2/FiO_2 ratio (≤200 mm Hg and >200 mm Hg). Within 1 h after the validation of inclusion criteria, patients were randomly assigned (1:1), with the use of a centralised web-based management system (G-ERDC, Clinfile, France), to one of either high-flow oxygen therapy or non-invasive ventilation.

Although individual patient assignments could not be masked, the coordinating centre and all the investigators remained unaware of the outcomes of each study group until the data were locked on Oct 11, 2017. Before locking the database and after trial completion, the blind review board (appendix) checked data and decided which patients could be included in the intention-to-treat analysis in accordance with the Good Clinical Practice Guidelines. An adjudication committee, who were unaware of the study groups, reviewed all the data on pulse oximetry that were recorded and stored to analyse the events occurring during the intubation procedure. An independent biostatistician—who was unaware of study outcomes and treatment allocation—collected patient data from the recordings and extracted pulse oximetry curves and values. All analyses were done by the study statistician in accordance with the International Conference on Harmonization and Good Clinical Practice Guidelines. The complete methodology of the study has been previously published.[18]

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	Non-invasive ventilation (n=142)	High-flow nasal cannula oxygen therapy (n=171)	p value
Age, years	64 (13)	64 (14)	0·74
Sex	..	..	0·24
Male	101 (71%)	111 (65%)	..
Female	41 (29%)	60 (35%)	..
Body-mass index, kg/m²	27 (7)	27 (6)	0·90
Simplified Acute Physiology Score II*	52 (20)	51 (19)	0·85
Sepsis-related Organ Failure Assessment at inclusion†	5 (3)	6 (3)	0·31
Underlying chronic lung disease	52 (37%)	53 (31%)	0·23
Past upper airway tract cancer	4 (3%)	4 (2%)	0·99
Reason for ICU admission	..	..	0·31
Respiratory primary failure			
Respiratory infection	50 (35%)	60 (35%)	..
COPD exacerbation	8 (6%)	8 (5%)	..
Extra-pulmonary ARDS	4 (3%)	2 (1%)	..
Pulmonary atelectasis	2 (1%)	2 (1%)	..
Other	17 (12%)	16 (9%)	..
Non-respiratory primary failure			
Shock	24 (17%)	42 (25%)	..
Cardiogenic pulmonary oedema	10 (7%)	7 (4%)	..
Neurologic	7 (5%)	6 (4%)	..
Other	13 (9%)	23 (13%)	..
Postoperative	7 (5%)	5 (3%)	..
Oxygen device the last hour before inclusion	..	..	0·90
Standard oxygen	63 (44%)	73 (43%)	..
High-flow nasal cannula oxygen therapy	48 (34%)	57 (33%)	..
Non-invasive ventilation	31 (22%)	41 (24%)	..
Vasopressor support at inclusion	27 (19%)	35 (20%)	0·75
Bilateral pulmonary infiltrates	88 (62%)	106 (62%)	0·98
Respiratory rate, breaths per min	30 (8)	31 (8)	0·35
PaO_2:FiO_2 ratio, mm Hg	142 (65)	148 (70)	0·40
Stratification sub-groups	..	..	0·06
PaO_2:FiO_2 ratio >200 mm Hg	25 (18%)	46 (27%)	..
PaO_2:FiO_2 ratio ≤200 mm Hg	117 (82%)	125 (73%)	..
MACOCHA score‡	..	..	0·83
<3	119 (84%)	144 (84%)	..
≥3	23 (16%)	26 (15%)	..
Cormack III or IV§	13 (9%)	16 (9%)	0·95
Intubation Difficulty Scale¶	..	..	0·53
≤5	121 (85%)	151 (88%)	..
>5	18 (13%)	18 (11%)	..

Data are mean (SD) or n (%). Reason for ICU admission was compared among three classes (respiratory primary failure, non-respiratory primary failure, and postoperative) via χ^2 tests. COPD=chronic obstructive pulmonary disease. ARDS=acute respiratory distress syndrome. *Calculated from 17 variables at inclusion, information about previous health status, and from information obtained at admission. Scores range from 0 to 163, with higher scores indicating more severe disease.[24] †Scores range from 0 to 24, with higher scores indicating more severe organ failure. ‡MACOCHA is calculated from seven variables: Mallampati score III or IV, apnoea syndrome, cervical spine limitation, opening mouth less than 3 cm, coma, hypoxia, and non-trained operator. Scores range from 0 to 12 points, with higher scores indicating higher risk of difficult intubation. §Cormack grade III is defined if no part of the glottis can be seen, but the epiglottis can be, grade IV is defined if not even the epiglottis can be exposed. ¶Scores are: 0, easy; 0–5, slight difficulty; and more than 5, moderate to major difficulty for intubation.

Table 1: **Baseline characteristics of the Intention-to-treat population, by study group**

Procedures

Preoxygenation was done in a semi-recumbent position at 30° for 3–5 min with the technique assigned by randomisation, regardless of the previous technique used for oxygenation. In the non-invasive ventilation group, preoxygenation was delivered via a face mask connected to an ICU ventilator. Pressure-support ventilation was adjusted to obtain an expired tidal volume between 6 mL/kg and 8 mL/kg of predicted bodyweight with a positive end-expiratory pressure of 5 cm H_2O and an FiO_2 of 1·0. Non-invasive ventilation therefore provided oxygenation and ventilation during preoxygenation and between induction and laryngoscopy, but neither oxygenation nor ventilation during laryngoscopy.

In the high-flow oxygen group, preoxygenation was delivered by applying oxygen continuously via binasal prongs, with a gas flow of 60 L/min through a heated humidifier (MR 850; Fisher & Paykel, Auckland, New Zealand) and an FiO_2 of 1·0. Clinicians performed a jaw thrust to maintain a patent upper airway, and continued high-flow oxygen therapy during laryngoscopy until the endotracheal tube was placed into the trachea. High-flow oxygen therefore provided oxygenation but little ventilation during preoxygenation, between induction and laryngoscopy, and also during laryngoscopy.

A management bundle for the intubation procedure was proposed to all of the participating centres (as previously described[4]), and included the presence of two operators, systematic fluid loading before intubation (isotonic saline or balanced crystalloids at the discretion of each patient's physician) in the absence of cardiogenic pulmonary oedema, and rapid-sequence induction using etomidate (0·2–0·3 mg/kg) or ketamine (1·5–3·0 mg/kg), combined with rocuronium (0·6–1·0 mg/kg) or succinylcholine (1·0 mg/kg). In cases of unsuccessful intubation, the following algorithm was proposed (with adaptations for local procedures): an introducer first (intubating stylet or Eschmann introducer), then videolaryngoscopy, an intubation laryngeal mask airway, and finally fibrescopy and rescue percutaneous or surgical tracheostomy. After endotracheal intubation, patients were mechanically ventilated with a tidal volume of 6 mL/kg of predicted bodyweight, a respiratory rate of 25–30 breaths per min, a positive end-expiratory pressure of 5 cm H_2O, and an FiO_2 set to maintain a pulse oximetry above 90%.

Outcomes

The primary outcome was the occurrence of an episode of severe hypoxaemia, defined as a decrease in pulse oximetry below 80% for at least 5 s, between the beginning of rapid-sequence induction (end of preoxygenation) and 5 min after confirmation of tracheal intubation by capnography; this outcome was assessed in the intention-to-treat population. To ensure that all centres monitored pulse oximetry equivalently, a dedicated portable pulse oximetry monitor (Nelcor DS 100A; Covidien, Dublin, Ireland) and single-use digital sensors (Max-A-I; Covidien)

were given to all participating centres. Pulse oximetry values were recorded with a 1 Hz frequency (one value of pulse oximetry by second) during the procedure and stored for subsequent analysis.

Secondary outcomes, which were collected at the bedside by physicians, residents, or nurses, were the value of pulse oximetry at the end of preoxygenation and the lowest value during the intubation procedure. Other prespecified outcomes were feasibility of preoxygenation evaluated by a four-point scale (easy, quite easy, quite difficult, difficult), Cormack grade,[19] intubation difficulty scale,[20] difficulty for intubation (more than two laryngoscopic attempts to place the endotracheal tube into the trachea or lasting more than 10 min using conventional laryngoscopy, MACOCHA score, and use of alternative management devices),[21,22] agitation, immediate complications (arterial hypotension, sustained cardiac arrhythmia, bradycardia, cardiac arrest, death, oesophageal intubation, regurgitation, gastric distension, dental injury, and new infiltrate on chest radiograph), and late complications (occurrence of ventilator-associated pneumonia, worsening of SOFA score[23] from days 1–7, duration of mechanical ventilation, length of stay in ICU, and mortality at day 28).

Statistical analysis

On the basis of the assumption that severe hypoxaemia episodes occur in 25% of patients preoxygenated with high-flow oxygen,[14,15] we calculated that enrolment of 320 patients would provide the study with 95% power to show an absolute difference of 15% percentage points in the primary outcome between the two groups,[4,16] at a two-sided alpha level of 0·05.

Analyses were performed in the intention-to-treat population and in prespecified subgroups determined by the stratification variable, moderate-to-severe hypoxaemic patients with a PaO_2/FiO_2 ratio equal to or below 200 mm Hg versus mild hypoxaemic patients with PaO_2/FiO_2 ratio above 200 mm Hg. Baseline characteristics in each study group were analysed as frequencies and percentages for categorical variables and as means and SDs for continuous variables, as appropriate.

We used an unadjusted χ^2 test to compare the primary outcome between the two groups. We assessed heterogeneity of treatment effects across these prespecified subgroups by testing for treatment-covariate interaction with the logistic regression model. In a sensitivity analysis, we analysed the primary outcome with adjustment for baseline oxygenation via logistic regression. We compared secondary outcomes using unadjusted χ^2 tests for categorical variables and Student's *t* test or Mann-Whitney test for continuous variables.

A two-tailed p value of less than 0·05 was statistically significant. No allowance for multiplicity was performed; all secondary outcomes should be considered exploratory. We used SAS software (version 9.4; SAS Institute, Cary, NC, USA) for all analyses.

	Non-invasive ventilation (n=142)	High-flow nasal cannula oxygen therapy (n=171)	Absolute difference estimate (95% CI)	p value
Primary outcome				
SpO_2 <80% during intubation procedure				
Number of patients	33 (23%)	47 (27%)	−4·2 (−13·7 to 5·5)	0·39
95% CI	(17–31)	(21–35)	..	..
Secondary outcomes				
Lowest SpO_2 during intubation procedure, %	87 (13)	84 (16)	3·0 (−0·3 to 6·3)	0·13
SpO_2 at the beginning of preoxygenation, %	95 (5)	95 (4)	0·0 (−1·0 to 1·0)	0·65
SpO_2 at the end of preoxygenation, %	97 (4)	96 (5)	1·0 (0·0 to 2·0)	0·08
Duration of laryngoscopy, min	..	..	..	0·86
<1	88 (63%)	105 (61%)	1·4 (−9·3 to 12·1)	..
1–3	40 (29%)	53 (31%)	−2·4 (−12·4 to 7·8)	..
>3	12 (9%)	13 (8%)	1·0 (−5·2 to 7·6)	..
Procedure of tracheal intubation				
Number of laryngoscopy attempts	..	..	..	0·75
One	113 (80%)	135 (79%)	0·6 (−8·5 to 9·5)	..
Two	22 (15%)	30 (18%)	−2·0 (−10·2 to 6·4)	..
Three or more, or >10 min	7 (5%)	6 (4%)	1·4 (−3·2 to 6·7)	..
First operator junior	26 (18%)	37 (22%)	−3·3 (−12·0 to 5·7)	0·46
Intervention of another skilled operator	38 (27%)	47 (27%)	−0·7 (−10·4 to 9·2)	0·89
Use of alternative management devices	16 (11%)	25 (15%)	−3·3 (−10·7 to 4·4)	0·38
Introducer	15 (11%)	22 (13%)	−2·3 (−9·4 to 5·1)	..
Other	2 (1%)	6 (4%)	−2·1 (−6·2 to 1·9)	..
Successful intubation	142 (100%)	171 (100%)	0·0 (0·0 to 0·0)	1·00
At least one episode of systolic arterial pressure <90 mm Hg	70 (50%)	86 (50%)	−1·0 (−12·0 to 10·0)	0·86
Serious adverse events				
Immediate complications				
At least one episode of systolic arterial pressure <90 mm Hg	70 (49%)	86 (50%)	−1·0 (−12·0 to 10·0)	0·86
Sustained cardiac arrhythmia	3 (2%)	3 (2%)	0·4 (−3·2 to 4·4)	0·99
Bradycardia	2 (1%)	3 (2%)	−0·3 (−3·8 to 3·4)	0·81
Cardiac arrest during and after intubation	1 (1%)	5 (5%)	−3·2 (−6·0 to 13·7)	0·23
Oesophageal intubation	8 (6%)	6 (4%)	2·1 (−2·7 to 7·5)	0·42
Regurgitation	0	2 (1%)	−1·1 (−4·2 to 1·6)	0·50
Gastric distension	11 (8%)	6 (4%)	4·2 (−0·9 to 10·1)	0·12
Dental injury	0	1 (1%)	−0·6 (−3·2 to 2·1)	0·99
Agitation	1 (0·7%)	0 (0%)	0·7 (−1·6 to 3·9)	0·45
New infiltrate on chest x-ray after intubation	28 (20%)	33 (19%)	0·4 (−8·3 to 9·4)	0·96
Late complications				
Ventilator-associated pneumonia within day 7	21 (15%)	18 (11%)	4·3 (−3·1 to 12·0)	0·26
Ventilator-associated pneumonia during stay in ICU	31 (22%)	35 (20%)	1·4 (−7·6 to 10·6)	0·77
Death at day 28	53 (37%)	58 (34%)	3·4 (−7·1 to 14·0)	0·53

(Table 2 continues on next page)

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See Online for appendix

This trial is registered with ClinicalTrials.gov, number NCT02668458.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Results

Between April 15, 2016, and Jan 8, 2017, 2079 patients were intubated in the 28 participating ICUs, and 322 were enrolled. After we excluded five patients with no recorded data, two who withdrew consent or were under legal protection, one who was not intubated, and one who had a cardiac arrest (as determined by the blind review board), 313 patients were included in the analysis (figure 1). 142 patients were assigned to non-invasive ventilation and 171 to high-flow oxygen therapy. The median interval between admission to ICU and randomisation was 1 day (IQR 0–2).

The baseline demographics of patients did not differ between the two groups (table 1, appendix). The mean settings in the non-invasive ventilation group were a pressure support level of 9 cm H_2O (SD 4), a positive end-expiratory pressure of 5 cm H_2O (0·5), and an FiO_2 of 0·99 (0·06), resulting in a tidal volume of 8·3 mL/kg (2·6) of predicted bodyweight. In the high-flow oxygen group, mean settings were a gas flow of 58 L/min (9) with an FiO_2 of 0·99 (0·08). Preoxygenation lasted 5 min (2) with non-invasive ventilation and 5 min (4) with high-flow oxygen (p=0·45).

33 (23%) of 142 patients had severe hypoxaemia after preoxygenation by non-invasive ventilation and 47 (27%) of 171 after high-flow oxygen (absolute difference –4·2%, 95% CI –13·7 to 5·5; p=0·39; table 2).

We noted a significant interaction between PaO_2/FiO_2 ratio at enrolment and treatment group with respect to the primary outcome ($p_{interaction}$=0·003; appendix). Consequently, we analysed results in two subgroups: patients with moderate-to-severe hypoxemia (PaO_2:FiO_2 equal to or below 200), and patients with mild hypoxemia (PaO_2:FiO_2 ratio above 200 mm Hg).

In patients with moderate-to-severe hypoxaemia (PaO_2/FiO_2 ≤200), severe hypoxaemia occurred in 28 (24%) of 117 patients in the non-invasive ventilation group and 44 (35%) of 125 in the high-flow oxygen group (absolute difference estimate –11·3%, –22·3 to 0·3, p=0·0553; table 3). In sensitivity analyses, the risk of severe hypoxaemia was lower with non-invasive ventilation than with high-flow oxygen after adjustment for PaO_2 at randomisation (patients with PaO_2/FiO_2 ≤200 mm Hg: adjusted odds ratio [OR] 0·56, 95% CI 0·32–0·99, p=0·0459; all patients: OR 0·8, 0·48–1·34 and adjusted OR 0·75, 0·45–1·27). In patients with mild hypoxaemia (PaO_2/FiO_2 >200 mm Hg), severe

	Non-invasive ventilation (n=142)	High-flow nasal cannula oxygen therapy (n=171)	Absolute difference estimate (95% CI)	p value
(Continued from previous page)				
Late outcomes				
SOFA score at day 1	8 (4)	8 (4)	0·0 (–0·9 to 0·9)	0·62
SOFA score at day 7	5 (4)	5 (3)	0·0 (–0·8 to 0·8)	0·82
Ventilator–associated pneumonia within day 7	21 (15%)	18 (10%)	4·3 (–3·1 to 12·0)	0·30
Duration of mechanical ventilation, days	9 (10)	10 (10)	–1·0 (–2·6 to 0·6)	0·47
Length of stay in ICU, days	13 (10)	12 (9)	1·0 (–1·1 to 3·1)	0·82

Data are mean (SD) or n (%), unless otherwise indicated. NIV=non-invasive ventilation. HFOT=high-flow nasal cannula oxygen therapy. SpO_2=pulse oximetry. SOFA=Sepsis-related Organ Failure Assessment. ICU=intensive care unit.

Table 2: **Outcomes in the intention–to–treat population, by treatment group**

	Severe-to-moderate hypoxaemia (PaO_2/FiO_2 ≤200 mm Hg)				Mild hypoxaemia (PaO_2/FiO_2 >200 mm Hg)			
	Non-invasive ventilation (n=117)	High-flow nasal cannula oxygen therapy (n=125)	Absolute difference estimate (95% CI)	p value	Non-invasive ventilation (n=25)	High-flow nasal cannula therapy (n=46)	Absolute difference estimate (95% CI)	p value
Primary outcome								
SpO_2 <80% during intubation procedure	28 (24%)	44 (35%)	–11·3 (–22·3 to 0·3)	0·0553	5 (20%)	3 (7%)	13·4 (–2·2 to 33·1)	0·1197
95% CI	16–32	27–44	..	..	4–36	0–14	..	..
Adjusted on PaO_2	..	..	..	0·0459	..	..	..	0·1003
Secondary outcomes								
SpO_2 at the beginning of preoxygenation	94% (5)	94% (4)	0·0 (–1·1 to 1·1)	0·75	97% (3)	97% (4)	0·0 (–1·8 to 1·8)	0·36
SpO_2 at the end of preoxygenation	97% (4)	96% (6)	1·0 (–0·0 to 2·0)	0·02	99% (3)	98% (4)	1·0 (–0·8 to 2·8)	0·31
Lowest SpO_2 during intubation procedure	86% (12)	81% (17)	5·0 (1·2 to 8·7)	0·02	90% (15)	93% (8)	–3·0 (–8·4 to 2·4)	0·31

Data are n (%) or mean % (SD), unless otherwise indicated. SpO_2=pulse oximetry.

Table 3: **Outcomes in the intention-to-treat population, by subgroup of stratification and treatment group**

hypoxaemia did not differ between the two groups (adjusted OR 3·60, 0·78–16·60).

Pulse oximetry values, duration of laryngoscopy, or procedure of tracheal intubation did not differ between the two preoxygenation groups (table 2). For the lowest pulse oximetry during the intubation procedure, there was also an interaction between PaO_2/FiO_2 at enrolment and treatment group ($p_{interaction}$=0·047; appendix).

In patients with moderate-to-severe hypoxaemia, the lowest pulse oximetry during intubation was higher in the non-invasive ventilation group than in the high-flow oxygen group (p=0·02; table 3, figure 2, appendix). Pulse oximetry at the end of preoxygenation was higher in the non-invasive ventilation group than in the high-flow oxygen group (p=0·02; table 3).

In patients with mild hypoxaemia, pulse oximetry at the end of preoxygenation and during intubation did not differ between the two groups (table 3, figure 2, appendix).

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

Preoxygenation was stopped in three patients during non-invasive ventilation and in six during high-flow oxygen therapy, mainly due to severe hypoxaemia (five of nine patients). The incidence of immediate and late complications did not differ between the two treatment groups (table 2). The most common immediate complications were systolic arterial hypotension and chest infiltrate on x-ray, and the most common late complications were death at day 28 and ventilator-associated pneumonia during ICU stay (table 2). Cumulative probability of survival did not differ between the two treatment groups, regardless of patient subgroups (table 2, appendix).

Discussion

In this multicentre, randomised, open-label trial of patients with acute hypoxaemic respiratory failure (defined as a PaO_2/FiO_2 ratio of ≤300 mm Hg), when compared with high-flow oxygen therapy, preoxygenation with non-invasive ventilation did not change the risk of severe hypoxaemia during intubation or the occurrence of late complications. Baseline PaO_2/FiO_2 ratio modified the effect of preoxygenation strategies on the risk of severe hypoxaemia, with secondary analyses suggesting a possible benefit of non-invasive ventilation among patients with moderate-to-severe hypoxaemia.

When designing the study, we assumed a reduction of severe hypoxaemia from the usual 25% to 10%. Although this reduction could seem optimistic, most studies report severe hypoxaemia in 25% of patients treated with high-flow oxygen or standard oxygen preoxygenation.[3,13–15] In the non-invasive ventilation group, we based our estimation of severe hypoxaemia on two previous studies reporting an incidence of 10% or less.[4,16]

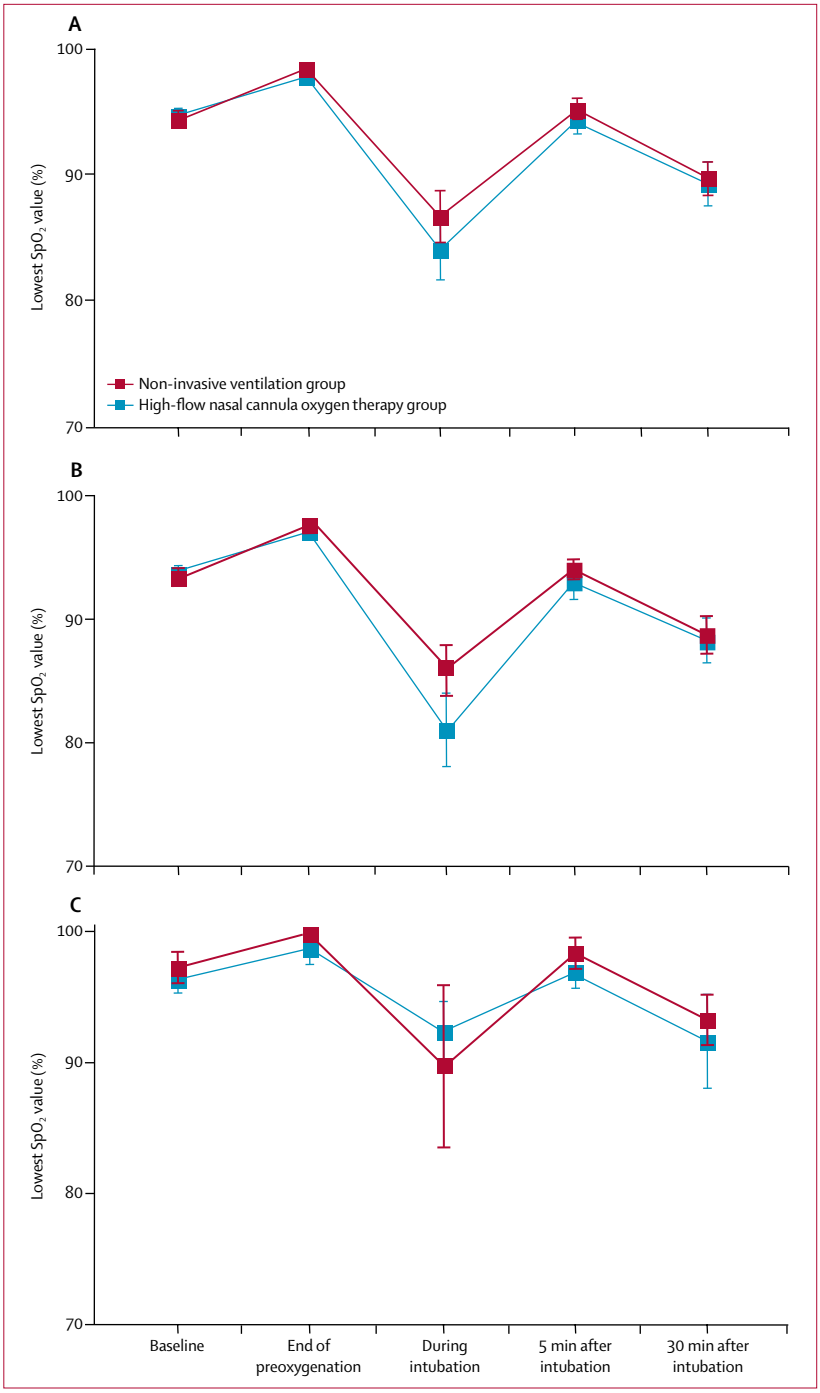

Figure 2: **Changes in minimal pulse oximetry from baseline to the end of the intubation procedure**
Data are mean values for the overall population (A), patients with moderate-to-severe hypoxaemia (PaO_2/FiO_2 ≤200 mm Hg; B), and patients with mild hypoxaemia (PaO_2/FiO_2 >200 mm Hg; C). Error bars are 95% CIs.

Our results showed that about 25% of patients in both groups had severe hypoxaemia. Accurate offline analysis of pulse oximetry recordings during the whole intubation procedure using a dedicated monitor might have identified otherwise unrecognised events and subsequently increased the rates of severe hypoxaemia.

Given that intubation is a sometimes urgent, difficult, and confusing procedure, it can be difficult to detect all episodes of severe hypoxaemia, which could lead to an underestimation of events.

There was an imbalance in stratification factors, especially in the patients with mild hypoxaemia. The observed imbalance was 21 patients in this stratum, which can be explained by the stratification of patients according to the PaO_2/FiO_2 ratio and to centres who randomly allocated patients to treatment in permuted blocks of four. The maximum theoretical imbalance between the two groups of treatment for a given stratum in a given centre was two patients. Given that 21 among the 28 participating centres have included patients in this stratum, the final imbalance could have been 42 patients.

To explore the effects of preoxygenation strategies in hypoxaemic patients, we planned our subgroups analysis according to the severity of hypoxaemia based on the classification of acute respiratory distress syndrome (moderate-to-severe versus mild).[25] These predefined subgroups included strata determined by PaO_2/FiO_2 ratio (≤200 mm Hg and >200 mm Hg) at randomisation, regardless of the oxygen device applied before preoxygenation. Our results showed that treatment had differing effects across these two predefined subgroups (ie, a benefit in one subgroup and harm in another) for severe hypoxaemia, supported by a significant test of interaction.[26] The effect of non-invasive ventilation on severe hypoxaemia differed according to the prespecified subgroup after adjustment for baseline oxygenation, and appeared to be beneficial during preoxygenation only in patients with moderate-to-severe hypoxaemia.

No previous studies have compared the effects of non-invasive ventilation with those of high-flow oxygen. In three randomised controlled studies,[13–15] high-flow oxygen (usually set with a gas flow of 50 L/min and an FiO_2 of 100%) was compared with standard oxygen preoxygenation, but high-flow oxygen has never been found to be superior to standard preoxygenation with valve-bag mask. One pilot study[16] that included 53 patients found that non-invasive ventilation was superior to valve-bag mask during preoxygenation in avoiding risk of severe hypoxaemia and obtaining higher pulse oximetry. However, none of these studies evaluated the effects of preoxygenation strategies according to the level of oxygenation in patients with respiratory failure. Another study[17] showed that non-invasive ventilation during preoxygenation was more efficient than valve-bag mask oxygen was at preventing severe hypoxaemia in patients previously treated with non-invasive ventilation. One explanation might be that these patients had more severe hypoxaemia than those treated with oxygen only. Our study showed that non-invasive ventilation was beneficial for preoxygenation of patients with the most severe hypoxaemia.

The significantly increased pulse oximetry at the end of preoxygenation with non-invasive ventilation might explain its potential positive effect during preoxygenation among patients with moderate-to-severe hypoxaemia. Physiological effects of non-invasive ventilation include the ability to rapidly improve[16] oxygenation in a similar manner to invasive ventilation,[27] through delivery of high levels of FiO_2 and intrathoracic positive pressures favouring the increase of lung volumes or alveolar recruitment.[9] High-flow oxygen might have a similarly rapid effect—ie, positive end-expiratory pressure effect with an increased end-expiratory lung volume[28]—but with a lower magnitude than non-invasive ventilation.[8,10] High-flow oxygen can generate a positive end-expiratory pressure of 1–3 cm H_2O in patients with respiratory failure, which is lower than that reported with non-invasive ventilation.[29] Consequently, for the prevention of hypoxaemia, the effect of apnoeic oxygenation during laryngoscopy under high-flow oxygen is not as efficient as high positive pressures delivered by non-invasive ventilation.

Preoxygenation strategies had no effect on mortality, regardless of the subgroup of patients. In fact, during the intubation procedure, risk of mortality is highest during the procedure or immediately after starting the mechanical ventilation, especially in patients with severe hypoxaemia. However, there was no evidence of delayed mortality in our Kaplan-Meier curves in this study.

Our trial has various strengths, including the multicentre design, sealed randomisation to the assigned treatment, subgroups analysis enabling the detection of differences across strata, a well defined protocol that included the adjudication of downloaded pulse oximetry recordings of each patient with the same dedicated portable pulse oximetry monitor among centres, complete follow-up at 28 days, and an intention-to-treat analysis. These strengths suggest the results are generalisable to most patients with acute hypoxaemic respiratory failure requiring intubation in ICUs.

Our study has several limitations. First, we did not consider a strategy of preoxygenation with a valve-bag mask in the control group. Given that high-flow oxygen therapy has showed efficacy in the management of patients with acute respiratory failure,[10] and is at least as efficient as valve-bag mask for preoxygenation,[12,15] most investigators of the study were concerned about switching to preoxygenation with a valve-bag mask, which could be potentially less effective at improving oxygenation.[12] Second, a high proportion of patients who were intubated in ICUs during the study period were not included, which could restrict the generalisation of our findings. Many of the patients excluded from the study were not hypoxaemic, underwent urgent intubation, had a cardiac arrest, or were in a coma. However, cardiac arrest and coma are not frequent reasons for intubation during acute hypoxaemic respiratory failure and are contraindications to non-invasive ventilation; therefore, exclusion of these patients is unlikely to have affected our results.[10] Third, our primary outcome was not mortality;[30]

however, most randomised, controlled studies[13–17,31] to date have assessed hypoxaemia as their primary outcome, which is a surrogate endpoint for hypoxia-driven cardiac arrests.[32] Finally, treatment allocation could not be concealed. To mitigate this limitation, pulse oximetry curves were recorded and downloaded for evaluation by adjudicators masked to treatment allocation to analyse the events occurring during intubation.

In summary, preoxygenation with non-invasive ventilation or high-flow oxygen therapy during intubation did not change the risk of severe hypoxaemia and other immediate or late complications in patients with acute hypoxaemic respiratory failure. However, compared with high-flow oxygen, non-invasive ventilation might better prevent severe hypoxaemia among patients with severe-to-moderate hypoxaemia. This finding warrants further research.

Contributors

J-PF was the lead investigator of the study, designed the study, was a member of the steering committee, and was responsible for data acquisition and collection, data analysis and interpretation, and drafting of the manuscript. J-DR and AWT were responsible for study design, data acquisition and collection, data analysis and interpretation, drafting of the manuscript, and critical revisions of the manuscript. SR analysed and interpreted the data. All other authors were responsible for data acquisition and collection and critical revisions of the manuscript.

Declaration of interests

J-PF reports grants from the French Ministry of Health; grants, personal fees, and non-financial support from Fisher & Paykel Heathcare, during the conduct of the study; and personal fees and non-financial support from SOS Oxygene, outside of the submitted work. J-DR reports travel and accommodation expenses from Fisher & Paykel Healthcare. AD reports grants from the French Ministry of Health; personal fees and non-financial support from Medtronic; grants, personal fees, and non-financial support from Philips; grants and personal fees from Resmed and Fisher & Paykel Healthcare; and personal fees from Baxter and Hamilton. RC reports travel expenses from Merck Sharpe, and Dohme and Fisher & Paykel Healthcare, outside of the submitted work. PED reports personal fees from Fisher & Paykel Heathcare outside of the submitted work. SE reports unrestricted research grants from Fisher & Paykel Healthcare, Hamilton, and Aerogen; consultancy and travel expenses from Aerogen, La Diffusion Technique Française, and Baxter; and travel expenses from Fisher & Paykel Healthcare. CG reports grants and non-financial support from Fisher & Paykel Healthcare, during the conduct of the study, personal fees from Fisher & Paykel Healthcare, and non-financial support from Resmed, outside of the submitted work. AWT reports travel and accommodation expenses from Covidien, General Electric Healthcare, Fisher & Paykel Healthcare, and Maquet. All other authors declare no competing interests.

Data sharing

No further data are available.

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