Intensive Care Med (2015) 41:1538–1548
DOI 10.1007/s00134-015-3796-z

SEVEN-DAY PROFILE PUBLICATION

Mickaël Vourc'h
Pierre Asfar
Christelle Volteau
Konstantinos Bachoumas
Noëmie Clavieras
Pierre-Yves Egreteau
Karim Asehnoune
Alain Mercat
Jean Reignier
Samir Jaber
Gwenaël Prat
Antoine Roquilly
Noëlle Brule
Daniel Villers
Cédric Bretonniere
Christophe Guitton

High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled clinical trial

Received: 18 February 2015
Accepted: 2 April 2015
Published online: 14 April 2015

The data were presented in preliminary format at the 43rd international congress of the French Reanimation society in January 2014.

Take-home message: Intubation in hypoxemic patients is a high-risk event. Preoxygenation contributes to the safety of the procedure. Strategies to decrease deep desaturation during intubation in hypoxemic patients have been little studied. Despite theoretical advantages and widespread use, randomized studies have never evaluated high-flow therapy in preoxygenation before intubation for hypoxemic patients. This study shows that this new device, maintained in place from the beginning of preoxygenation to the end of the intubation procedure, does not prevent deep desaturation during intubation in severely hypoxemic patients.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-3796-z) contains supplementary material, which is available to authorized users.

M. Vourc'h · N. Brule · D. Villers · C. Bretonniere · C. Guitton (✉)
Medical Intensive Care Unit, Hôtel-Dieu, University Hospital of Nantes, 30 bd Jean Monnet, 44093 Nantes, France
e-mail: christophe.guitton@chu-nantes.fr
Tel.: +33-2-40087365

P. Asfar · A. Mercat
Medical Intensive Care and Hyperbaric Medicine Department, Angers University Hospital, University of Angers, 49933 Angers, France

C. Volteau
Biometry Platform, Research Promotion Department, University Hospital of Nantes, 30 bd Jean Monnet, 44093 Nantes, France

K. Bachoumas · J. Reignier
Medical-Surgical Intensive Care Unit, District Hospital Centre, 85925 La Roche/Yon, France

N. Clavieras · S. Jaber
Medical-Surgical Intensive Care Unit, University Hospital of Montpellier and INSERM U1046, 34295 Montpellier, France

P.-Y. Egreteau · G. Prat
Medical Intensive Care Unit, University Hospital Cavale Blanche of Brest, bd Tanguy Prigent, 29609 Brest, France

K. Asehnoune · A. Roquilly
Department of Anaesthesiology, Hôtel-Dieu, University Hospital of Nantes, 44093 Nantes, France

K. Asehnoune · A. Roquilly
Department of Surgical Intensive Care, Hôtel-Dieu, University Hospital of Nantes, 44093 Nantes, France

C. Guitton
INSERM UMR1064, 30 bd J. Monnet, 44093 Nantes Cedex 01, France

Abstract: *Purpose:* Intubation of hypoxemic patients is associated with life-threatening adverse events. High-flow therapy by nasal cannula (HFNC) for preoxygenation before intubation has never been assessed by randomized study. Our objective was to evaluate the efficiency of HFNC for preoxygenation, compared to high fraction-inspired oxygen facial mask (HFFM). *Methods:* Multicenter, randomized, open-labelled, controlled PREOXYFLOW trial (NCT 01747109) in six French intensive care units. Acute hypoxemic adults requiring intubation were randomly allocated to HFNC or HFFM. Patients were eligible if PaO_2/FiO_2 ratio was below 300 mmHg, respiratory rate at least 30/min and if they required FiO_2 50 % or more to obtain at least 90 % oxygen saturation. HFNC was maintained throughout the procedure, whereas HFFM was removed at the end of general anaesthesia induction. Primary outcome was the lowest saturation throughout intubation procedure. Secondary outcomes included adverse events related to intubation, duration of mechanical ventilation and death. *Results:* A total of 124 patients were randomized. In the intent-to-treat analysis, including

119 patients (HFNC $n = 62$; HFFM $n = 57$), the median (interquartile range) lowest saturation was 91.5 % (80–96) for HFNC and 89.5 % (81–95) for the HFFM group ($p = 0.44$). There was no difference for difficult intubation ($p = 0.18$), intubation difficulty scale, ventilation-free days ($p = 0.09$), intubation-related adverse events including desaturation <80 % or mortality ($p = 0.46$). *Conclusions:* Compared to HFFM, HFNC as a preoxygenation device did not reduce the lowest level of desaturation.

Keywords Preoxygenation · High-flow oxygen therapy · Severe hypoxemia · Intubation

Introduction

Acute respiratory failure is a life-threatening condition in intensive care units (ICU) that often requires ventilator support after endotracheal intubation (ETI). In critically ill patients, ETI carries a higher risk than in elective surgery and can lead to mild to severe complications for 30 % of patients [1]. The most frequently reported complication is desaturation below 80 % (26 %). Severe hypoxemia before ETI has been reported as an independent risk factor of severe desaturation during intubation in ICU [2].

Preoxygenation with a high fraction-inspired oxygen facial mask (HFFM) is recommended to delay arterial desaturation during intubation apnoea [2–4]. The quality of preoxygenation contributes to the safety of the procedure. Nevertheless, it is sometimes ineffective in critically ill patients, especially in hypoxemic patients. Despite well-conducted preoxygenation, desaturation <80 % occurs in a quarter of hypoxemic patients [2]. Non-invasive ventilation (NIV) seems to improve preoxygenation in this population, but these results have not been confirmed in large studies [5].

High-flow therapy by nasal cannula (HFNC) is a new device that provides almost pure oxygen with FiO_2 of about 100 %, up to 60 l/min [6]. HFNC seems to generate low positive airway pressure [7, 8], and holding nasal prongs in place after rapid sequence intubation during laryngoscopy could enable operators to perform apnoeic oxygenation and reduce desaturation during ETI [9]. A recent before–after study suggests its ability to improve preoxygenation and to reduce severe hypoxemia during ETI [10].

Although HFNC is widespread, randomized studies have never evaluated this device during preoxygenation. We therefore conducted a multicenter, randomized, controlled trial comparing HFNC and HFFM in preoxygenation before ETI in ICU hypoxemic patients (PREOXYFLOW study). We postulated that HFNC was more efficient than HFFM desaturation during ETI. The secondary objectives were to determine whether HFNC could reduce complications during ETI, and improve morbidity in ICUs.

Methods

Study design, setting, and ethical considerations

PREOXYFLOW is a multicenter, randomized, controlled, parallel, open-label study comparing two preoxygenation strategies for ETI in ICUs. The main objective was to determine whether HFNC was more effective than HFFM in reducing desaturation during ETI after rapid sequence induction.

Patients were enrolled from December 2012 to August 2013 in six French ICUs (three medical, two medical-surgical and one surgical). An independent safety committee oversaw the trial.

Three methods of consent were available. Hypoxemia often prevented the patient from understanding information. Thus, most patients were included after written informed consent was provided by next of kin or an emergency procedure (investigator signature) if next of kin were not immediately available or if there was not enough time before ETI. When available, patients were retrospectively asked for written consent to continue the trial after recovery. Only a few patients were included after self-consent. The ethics committee ("Comité de Protection des Personnes Ouest II" from Angers, France) approved this study protocol on 9 October 2012 (CPP ref. 2012/17).

Randomization

Randomization used fixed blocks of four patients (ratio 1:1) and was stratified by centre. The study statistician generated the allocation list. Patients were allocated to one of the two preoxygenation strategies (HFNC or HFFM) using a secure computer-generated online remote system (Clinisight software) controlled by the independent research promotion unit at the University Hospital of Nantes, which had no role in patient recruitment. Day 1 was the day of inclusion and randomization.

Patients

Eligible patients were adults (18 years or older) with acute hypoxemic respiratory failure, requiring ETI in ICU

after rapid sequence induction (prompt general anaesthesia induction and subsequent intubation). Acute hypoxemic respiratory failure was defined as a respiratory rate higher than 30 per minute and a FiO_2 requirement of 50 % or more to obtain at least 90 % oxygen saturation, and an estimated PaO_2/FiO_2 ratio below 300 mmHg, in the 4 h before inclusion.

Exclusion criteria were: contraindication to orotracheal intubation; intubation without anaesthetic rapid sequence induction; ETI for cardiac arrest; asphyxia requiring immediate ETI; nasopharyngeal obstacle; Grade 4 glottis exposure on the Cormack–Lehane scale, adults subject to a legal protection scheme; pregnancy or lack of consent.

Intervention: preoxygenation and intubation procedure

The patients were randomized immediately after inclusion. In the intervention group (HFNC), preoxygenation was performed for 4 min with high-flow nasal cannula (Optiflow^{TM}; Fisher & Paykel Healthcare, Auckland, NZ) set to 60 l/min of humidified oxygen flow (FiO_2 100 %) [11]. In this group, after induction, the nasal cannulae were maintained in place throughout the ETI, in an attempt to achieve apnoeic oxygenation. In the control group (HFFM), preoxygenation was performed for 4 min with high FiO_2 facial mask (15 l/min oxygen flow) [5, 12]. After general anaesthetic induction, the HFFM was removed, enabling laryngoscopy vision.

The patients were intubated according to international recommendations and standard practices at each participating ICU [13]. Patients receiving non-invasive ventilation (NIV), HFFM or HFNC at the time of randomization were switched to their randomly assigned device at the beginning of the preoxygenation procedure. The PREOXYFLOW Study design is summarized in online-only material (see Fig. E1).

Endpoints

The primary outcome was the lowest saturation measured by continuous pulse oximetry (SpO_2) during ETI, from the end of rapid sequence induction (beginning of laryngoscopy) to patient connection to mechanical ventilation (see Fig. E1). To improve the quality of data collection, an external observer and the nurse in charge of the patient concurrently assessed this endpoint.

The secondary outcomes were: quality of preoxygenation, including duration, ability of the device to improve SpO_2; the quality of the ETI procedure, including adverse events during ETI and in the next hour, difficult intubation rate and intubation difficulty score (IDS); organ failure during the first 5 days (SOFA score); PaO_2/FiO_2 ratio during the following hour and the first 5 days; morbidity in ICU (time on ventilator, length of stay, ventilation-free days, occurrence of ventilator-associated pneumonia and mortality rate on day 28) [14].

Difficult intubation was defined as three or more laryngoscopies attempts or the need to use alternative devices, or procedure duration longer than 10 min. Adverse events were classified as severe complications (death, cardiac arrest, desaturation <80 %; severe collapse defined by systolic blood pressure <80 or vasopressor introduction or increasing doses more than 30 %) or mild to moderate complications (severe ventricular or supraventricular arrhythmia requiring intervention, oesophageal intubation, dangerous agitation with Richmond agitation scale >3, vomiting with aspiration of gastric content, dental injury). All patients were followed until discharge from ICU and up to day 28. An independent monitoring board analyzed the data.

Sample size

The primary outcome was the lowest SpO_2 during ETI up to connection to mechanical ventilation. The trial was designed to detect an increase of 6 % in SpO_2 from 85 % in the HFFM group to 91 % in the HFNC group. As no data were available, this hypothesis was based on previous results comparing NIV to HFFM [5]. With 80 % power, a 5 % type I error (two-sided) and 2 % attrition rate, the required sample size was 122 patients. A few weeks after the beginning of the study, two patients had to be excluded on the basis of exclusion criteria. Thus, the independent steering committee decided to increase the sample size to 124 in order to preserve the power of the study.

Statistical analysis

Analyses were performed in an intent-to-treat population including all the randomized patients except two patients who withdrew their consent, two patients who did not meet the inclusion criteria and one patient who improved before ETI.

Baseline characteristics were described for each group. Continuous variables were presented with mean and standard deviation, or median and interquartile range, when the assumption of normality was not met. Categorical data were expressed as numbers and percentages.

The primary outcome was compared between the two groups using the Van Elteren test (non-parametric test taking randomisation stratified by centre into account). Sensitivity analyses were performed a posteriori: the main criterion was lacking for one patient in the HFFM group, so analysis with best-case imputation was performed. Analysis was completed by four sensitivity tests with adjustment to baseline saturation or baseline PaO_2/FiO_2, to SpO_2 at the beginning of preoxygenation or SpO_2 at the end of preoxygenation.

The secondary outcomes were compared between groups with generalised linear mixed models (logistic

regression) or nonparametric Van Elteren Tests for the quantitative outcome, to take stratification into account. For SpO_2 at the end of preoxygenation, an adjustment was made on SpO_2 at the beginning of preoxygenation. The proportions of patients with severe and moderate complications in the two groups were compared using the Chi square or Fisher tests.

Statistical tests were two-sided, with a statistical significance of $p < 0.05$. SAS software v.9.3® was used for all statistical analyses.

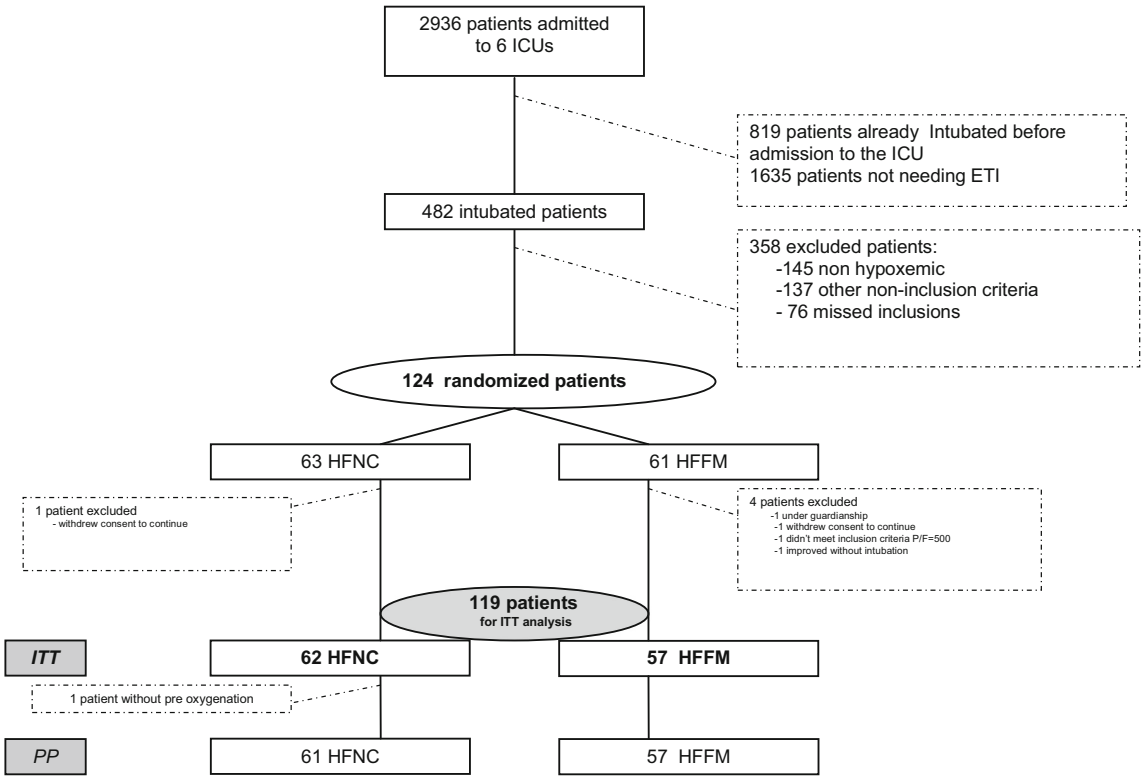
Results

Patients

Between December 2012 and August 2013, 2936 patients were admitted. Out of 482 patients who underwent ETI on admission or during their stay in the ICU, 124 with hypoxemic respiratory failure were included for randomization in the PREOXYFLOW study (Fig. 1). Five patients were excluded (two withdrew consent, two major inclusion criteria deviations, one patient improved before ETI and was not intubated). Finally, 119 patients were included for the ITT analysis (62 in the HFNC group and 57 in the HFFM group). One patient in HFNC underwent ETI without preoxygenation due to extreme emergency.

The main baseline characteristics were similar between the two groups (Table 1). Infectious pneumonia was the main cause of respiratory failure on admission with 40.3 % in HFNC and 50.9 % in HFFM. At inclusion, the mean (SD) PaO_2/FiO_2 ratio was 120.2 (55.7) mmHg in HFNC and 115.7 (63) mmHg in the HFFM.

Airways and ETI are described in Table 2. Difficult facial mask ventilation and difficult intubation criteria were quite similar in the two groups.



HFNC: high flow nasal cannulae

HFFM: high FiO2 facial mask

ITT: intention to treat, PP: per protocol

Fig. 1 PREOXYFLOW study flow

Table 1 Baseline characteristics of the intent-to-treat population at inclusion

	High-flow nasal cannulae ($n = 62$)	High-flow face mask ($n = 57$)
Sex ratio M/F	39/23	39/18
Age, mean (SD), years	64.9 (14)	59.3 (14.5)
BMI, mean (SD)[a]	27.6 (5.8)	27.6 (7.3)
Medical patients, *n* (%)	54 (87.1)	50 (87.7)
SAPS II score, mean (SD)[b]	54.5 (20.2)	51.3 (16.5)
Comorbidities		
Chronic heart failure (NYHA III or IV), *n* (%)	4 (6.5)	3 (5.3)
Chronic respiratory failure, *n* (%)	5 (8)	5 (8.8)
Obstructive sleep apnoea syndrome, *n* (%)	1 (1.6)	6 (10.7)
COPD patients, *n* (%)[c]	7 (11.3)	6 (10.7)
Past upper airway tract cancer, *n* (%)	1 (1.6)	1 (1.8)
Diabetes requiring insulin therapy, *n* (%)	2 (3.2)	4 (7)
Vasopressor support at inclusion, *n* (%)	18 (29)	11 (19.3)
Glasgow Coma Score, mean (SD)	13.5 (2.8)	13.4 (2)
McCabe scale 2 or 3, *n* (%)[d]	30 (48.4)	23 (40.4)
Functional status KNAUS (class C or D), *n* (%)[e]	19 (30.6)	13 (22.8)
Respiratory failure aetiology, *n* (%)		
Pneumonia	25 (40.3)	29 (50.9)
Extra-respiratory ARDS	19 (30.6)	11 (19.3)
Cardiogenic pulmonary oedema	3 (4.8)	5 (8.7)
COPD exacerbation	4 (6.4)	0
Thoracic trauma	1 (1.6)	5 (8.7)
Other	10 (16.1)	7 (12.2)
Advanced oxygenation support in the last hour before inclusion, *n* (%)		
NIV	11 (17.8)	8 (14)
HFNC	10 (16.1)	3 (5.3)
Arterial blood gas oxygenation		
PaO_2/FiO_2, mean (SD), mm Hg	120.2 (55.7)	115.7 (63)
$PaCO_2$, mean (SD), mm Hg	39.8 (14.7)	37.4 (11)
SpO_2, mean (SD), %	94.6 (4.7)	93.4 (6)

HFNC high-flow therapy by nasal cannulae, *BMI* body mass index, *ARDS* acute respiratory distress syndrome, *SAPSII* simplified acute physiological score, *COPD* chronic obstructive pulmonary disease, *NIV* non-invasive ventilation

[a] Calculated as weight in kilograms divided by height in meters squared

[b] Used to assess the severity of illness: range 0–194, with higher scores indicating higher risk of death

[c] COPD was considered if obstructive syndrome had been documented on functional explorations

[d] McCabe classification: cat 1, nonfatal disease; cat 2, ultimately fatal disease (within 4 years); cat 3, rapidly fatal disease

[e] Knaus chronic health status: Class A, normal health status; Class B, moderate activity limitation; Class C, severe activity limitation due to chronic disease; Class D, bedridden patient

Primary outcome: lowest oxygen saturation during the ETI Procedure

In the ITT analysis (Table 3), there was no statistical difference regarding the lowest recorded SpO_2 during ETI comparing the HFNC group median (IQR), 91.5 % (80–96), versus the HFFM group, 89.5 % (81–95), $p = 0.44$. Both groups exhibited wide variability in lowest SpO_2 values (Fig. 2). As data were missing for one patient for the main criteria in HFFM group, a sensitivity analysis was performed with best-case imputation ($SpO_2 = 100$ %), with no difference between the two groups ($p = 0.55$). Considering the influence of the severity of acute respiratory failure, analyses were carried out with four other a posteriori sensitivity tests, with adjustment on PaO_2/FiO_2 on inclusion, SpO_2 on inclusion, and SpO_2 at the beginning and end of the preoxygenation phase. None of these analyses found any difference between HFNC and HFFM ($p = 0.85$, $p = 0.60$, $p = 0.49$ and $p = 0.79$, respectively).

Secondary outcomes

The secondary outcomes are reported in Table 3.

Oxygenation during preoxygenation

The 4-min preoxygenation phase was completed in 58 (93.5 %) patients in HFNC and 54 (94.7 %) in HFFM ($p = 0.83$). Along preoxygenation, mean (SD) SpO_2 rose slightly from 95.4 (3.9) to 97.1 (3.8) in the HFNC group and from 94.1 (6) to 96.3 (4.4) in the HFFM group with no difference in the delta SpO_2 ($p = 0.98$). The duration of preoxygenation did not influence the lowest SpO_2

Table 2 Airway, operators and emergency ETI procedure

	High-flow nasal cannulae ($n = 62$)	High-flow face mask ($n = 57$)
Airway description		
At least 2 difficult mask ventilation criteria[a], *n* (%)	43 (69.4)	33 (57.9)
Medical history of difficult intubation, *n* (%)	0	2 (3.5)
Mouth opening less than 3 cm, *n*/*n* tot[b] (%)	4/52 (7.7)	8/48 (16.7)
Limitation of cervical mobility ≤35°, *n*/*n* total[b] (%)	2/44 (4.6)	8/42 (19)
Thyromental distance < 65 mm, *n*/*n* tot[b] (%)	4/51 (7.8)	10/40 (25)
Mallampati III or IV, *n*/*n* tot[b] (%)	10/39 (25.6)	12/32 (37.5)
Macocha score, *n* (%)[c]		
<3	25 (78.1)	11 (55)
≥3	7 (21.88)	9 (45)
First operator[d]		
Senior *n* (%)	11 (17.7)	16 (28)
Junior *n* (%)	51 (82.2)	41 (71.9)
Emergency intubation[e]		
Real emergency, *n* (%)	12 (19.3)	29 (50.8)
Relative emergency, *n* (%)	48 (77.4)	25 (43.8)
Deferred emergency, *n* (%)	2 (3.2)	3 (5.2)
ETI drugs[f]		
Hypnotic agent, *n* (%)		
Etomidate	35 (56.5)	30 (52.6)
Ketamine	21 (33.9)	17 (29.8)
Others	13 (21)	15 (26.3)
Neuromuscular blocking agent, *n* (%)		
Succinylcholine	45 (72.6)	44 (77.2)
Rocuronium	10 (16.1)	7 (12.3)
Others	8 (12.9)	5 (8.8)
None	4 (6.5)	7 (12.3)

ETI endotracheal intubation, *HFNC* high-flow therapy by nasal cannulae

[a] Age >55 years, BMI >26, TM distance <6 cm, snoring, beard, lack of teeth, limitation of mandibular protrusion

[b] Some patients were not evaluated regarding these criteria before intubation because of the emergency of the ETI procedure (*n tot* number of patients for whom data was assessed)

[c] Macocha [1] score is used to predict difficult intubation; range 0–12 (higher scores predict more difficult intubation), missing data for 30 patients in HFNC and 37 in HFFM

[d] Residents were considered as junior operators. Doctors of medicine (MD) were considered as seniors

[e] Emergency intubation: *Real* requiring intubation without any delay; *Relative* requiring intubation within 1 h; *Deferred* requiring intubation in more than 1 h

[f] Some patients received several drugs

during ETI (see Table E1). Preoxygenation did not succeed in raising SpO_2 above 90 % ($p = 0.49$) in only four patients (6.5 %) in HFNC and 2 (3.5 %) in HFFM.

Description of the ETI procedure

All randomized patients were successfully intubated. Maintaining the HFNC in place did not increase the rate of difficult intubation: 1.6 and 7.1 %, respectively, in HFNC and HFFM ($p = 0.18$). The median (IQR) IDS score was similar 3 (2–4) in both groups ($p = 0.63$).

Outcome in ICUs

Patients in HFNC saw a significantly shorter median (IQR) duration of mechanical ventilation of 6 (4–14) days than those in HFFM of 10 (5–17) days ($p = 0.02$). However, there was no difference on day 28 of ventilator-free days ($p = 0.09$), SOFA score during the first 5 days, length of ICU stay or ventilator-associated pneumonia. The mortality rate on day 28 was 35.4 and 42.1 % in HFNC and HFFM ($p = 0.46$), respectively.

Complications during the ETI procedure and the following hour (Table 4)

At least one complication occurred in 36 (58.1 %) and 39 (68.4 %) patients in HFNC and HFFM ($p = 0.24$), respectively. At least one severe complication occurred in 36 (58.1 %) patients in HFNC and 38 (66.7 %) patients in HFFM ($p = 0.33$). Severe desaturation ($SpO_2 < 80$ %) was the main severe complication, with 16 (25.8 %) patients in HFNC and 13 (22.3 %) in HFFM ($p = 0.70$). Only one cardiac arrest was observed in the whole population during ETI. No patient died during ETI or over the next hour. No injury or unexpected effect related to the HFNC device was observed.

Table 3 Primary and secondary outcomes

	High-flow nasal cannulae ($n = 62$)	High-flow face mask ($n = 57$)	p[a]
Primary outcome			
Lowest SpO_2 during ETI procedure, median (IQR)	91.5 (80–96)	89.5 (81–95)	0.44
Secondary outcomes			
Preoxygenation			
Duration of preoxygenation, *n* (%)			
<4 min	4 (6.5)	3 (5.3)	
4 min or more	58 (93.5)	54 (94.7)	0.83
SpO_2 at the beginning of preoxygenation, mean (SD)	95.4 (3.9)	94.1 (6.0)	0.15
SpO_2 at the end of preoxygenation, mean (SD)	97.1 (3.8)	96.3 (4.4)	0.98
Failure to increase saturation to 90 % during preoxygenation, *n* (%)	4 (6.5)	2 (3.5)	0.49
ETI procedure			
Duration of ETI procedure, median (IQR), minutes	1 (0.7–1.3)	1 (0.7–2)	0.33
Cormack III or IV exposure, *n* (%)	8 (13.1)	7 (12.3)	0.89
Number of alternative airway management devices, *n* (%)			
None	60 (96.8)	51 (89.5)	0.18
One	2 (3.2)	6 (10.5)	
Two or more	0	0	
Successful intubation	62 (100)	57 (100)	0.99
Difficult intubation, *n* (%)[b]	1 (1.6)	4 (7.1)	0.18
IDS score, median (IQR)[c]	3 (2–4)	3 (2–4)	0.63
Respiratory outcome			
PaO_2 1 h after ETI, median (IQR), mm Hg	98.2 (72–139.5)	89.5 (69.8–144)	0.94
Duration of mechanical ventilation, median (IQR), days	6 (4–14)	10 (5–17)	0.02
Ventilator-free days (day 28), median (IQR), days[d]	14 (0–22)	5 (0–16)	0.09
Ventilator-associated pneumonia, *n* (%)	6 (9.7)	8 (14)	0.62
Morbidity in ICU			
ICU length of stay, median (IQR), days	10 (6–16)	13 (7–24)	0.12
SOFA score, mean (SD)			
Day 1	8.8 (4.1)	9.2 (3.6)	0.57
Day 2 ($n = 112$)	8.5 (4)	9.3 (4.1)	0.65
Day 3 ($n = 103$)	7.1 (3.5)	8 (4.7)	0.63
Day 4 ($n = 99$)	6.1 (3.6)	7.3 (4.5)	0.23
Day 5 ($n = 95$)	5.6 (3.8)	6.8 (4.6)	0.21
Death in ICU, *n* (%)	21 (33.9)	23 (40.4)	0.46
Mortality at 28 days, *n* (%)	22 (35.4)	24 (42.1)	0.48

SOFA sequential organ failure assessment used to assess the degree of dysfunction of 5 organ systems: respiratory, cardiovascular, renal, neurologic, hepatic. Each subscore ranges from 0 (healthy) to 4 (maximum severity); the overall score ranges from 0 to 20, *ETI* endotracheal intubation, *ICU* intensive care unit, SpO_2 arterial saturation measured by pulse oximetry, PaO_2 partial pressure of oxygen in arterial blood

[a] For comparison between HFNC and HFFM groups

[b] Difficult intubation was defined as ETI duration longer than 10 min and/or 3 or more laryngoscopy attempts or use of an alternative device

[c] IDS score is calculated after ETI to evaluate difficulty of the intubation. IDS <5 mean slightly difficult intubation. IDS >5 mean moderate to major difficulty [14]

[d] Mean number of days from day 1 to day 28 during which patients had been breathing without any assistance

Discussion

The aim of the study was to compare HFNC preoxygenation to HFFM for intubation in severely hypoxemic patients. Using HFNC without discontinuation during an apnoeic period was not more effective in preventing desaturation, regardless of the severity of respiratory distress. Our results also confirm that ETI for hypoxemic patients in ICUs is risky, with more than 50 % of serious adverse events and 25 % of desaturation below 80 % irrespective of the preoxygenation device, despite low difficult intubation rate [2]. This trial focusing on the ETI procedure highlighted no difference regarding outcome in ICU.

This is the first clinical trial comparing HFNC and HFFM as preoxygenation devices in a randomised multicentre controlled design. It matches medical and surgical patients with experienced staff. Despite the hypoxemia, the emergency and risk of ETI, we succeeded in including 119 patients in six centres over a 9-month period.

Our results are in contradiction with a single centre trial, before–after design included incidental patients regardless of the reasons for intubation. For most of them, respiratory failure was not the main issue. This probably explains the difference in favour of HFNC [10].

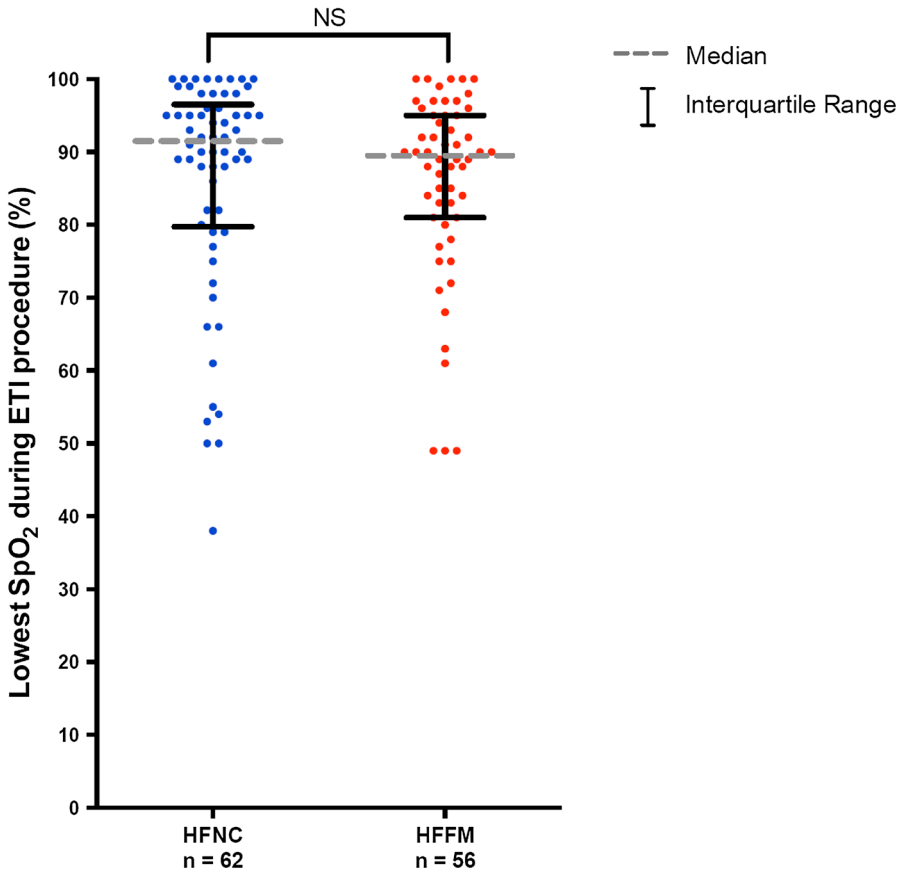


Fig. 2 Primary outcome: lowest SpO_2 during ETI procedure

HFNC: high flow nasal cannulae

HFFM: high FiO2 facial mask

HFNC exhibits several theoretical advantages. Firstly, this device was reported to improve oxygenation through high-flow oxygen and to create positive end expiratory pressure (PEEP) [15, 16]. Secondly, compared to a low-flow oxygen device, HFNC significantly increases the PaO_2/FiO_2 ratio and end expiratory lung volume in hypoxemic patients [17]. It may minimize desaturation during ETI. Thirdly, contrary to HFFM, HFNC can be maintained in place during ETI without restricting glottis catheter insertion. Considering that high oxygen flow may keep upper airways open, HFNC could lead to apnoeic oxygenation [7, 9, 18].

In our study, despite these theoretical advantages, HFNC did not seem to be more efficient than HFFM in preventing desaturation. Several reasons may explain these results. Our study included patients with severe hypoxemia (mean PaO_2/FiO_2 about 120 mmHg), and most of them suffered from pneumonia. HFNC only creates limited levels of PEEP [7, 19]. Non-invasive ventilation (NIV) might be an interesting alternative with higher PEEP levels. However, effects on functional respiratory capacity, especially during a 4-min preoxygenation, are unpredictable [20]. Extending preoxygenation for more than 4 min is not a better strategy either [11, 21]. Regarding apnoeic oxygenation, nasopharyngeal oxygen insufflation during ETI has been reported to improve the duration of apnoea without desaturation, only in studies with a small number of patients [9, 18]. Controversially, after general anaesthesia, as in obese or sleep apnoea patients, upper airway collapsing pressures dramatically increase [22–25]. This probably explains why HFNC failed to achieve apnoeic oxygenation during ETI.

Despite well-conducted randomization, the population at baseline in the two groups exhibited slight differences

Table 4 Incidence of ETI-related complications in each group (during the ETI procedure and the first hour post-procedure)

	High-flow nasal cannulae ($n = 62$)	High-flow face mask ($n = 57$)	p[a]
At least one complication, *n* (%)	36 (58.1)	39 (68,4)	0.24
At least one severe complication[b], *n* (%)	36 (58.1)	38 (66.6)	0.33
Desaturation <80 %[c]	16 (25.8)	13 (22.8)	0.70
Cardio-vascular collapse	24 (38.7)	30 (52.6)	0.13
Cardiac arrest	0	1 (1.8)	0.48
Death	0	0	
Moderate complications[d], *n* (%)			
Cardiac arrhythmia	0	0	
Oesophageal intubation	0	2 (3.5)	0.23
Agitation	0	1 (1.8)	0.48
Aspiration	0	0	
Dental injury	0	0	

ETI endotracheal intubation

[a] For comparison between HFNC and HFFM groups

[b] Severe complication definitions: desaturation <80 %; cardio-vascular collapse, systolic blood pressure <80 mmHg, vasopressor introduction or increasing doses more than 30 %, some patients presented with several severe complications

[c] Some patients underwent desaturation below 80 % after connection to mechanical ventilation. This explains why there are differences between Fig. 2 and Table 4 concerning this criterion

[d] Mild to moderate complications: cardiac arrhythmia, severe ventricular or supraventricular arrhythmia requiring intervention; oesophageal intubation; agitation, dangerous agitation with Richmond agitation scale >3; aspiration, vomiting with aspiration of gastric content

especially regarding difficult airway. Subgroups or multivariate analyses did not detect any influence on the primary outcome (data not shown).

The choice of the primary outcome can be discussed. We decided to consider minimal saturation instead of desaturations below 80 % in order to detect hypoxemic events regardless of their severity. Pulse oximetry is not as relevant and accurate as measured arterial oxygen saturation (SaO_2) or partial oxygen pressure (PaO_2) [26, 27]. Nevertheless, it is the only non-invasive, easily bedside-monitored criterion during everyday emergencies in ICU. It informs about apnoea tolerance and warns when to interrupt ETI. PaO_2 in an arterial blood gases test would have been a more reliable evaluation of blood oxygenation during and immediately after an ETI procedure. This would have required systematic catheterization to establish an indwelling arterial line, which seemed unthinkable due to the severity of the hypoxemia and level of ETI emergency. Moreover, given the very rapid variation, a research nurse was specifically dedicated to monitor SpO_2 throughout the procedure to improve data collection.

These negative results have to be balanced by power issues. Sample size calculation was based on reasonable hypothesis but settled by a single preliminary study [5]. We concede that our study is not an extensive trial but reflects pragmatic issues of ETI performed by trained operators in ICU. Further studies are needed to confirm these results in hypoxemic patients. The choice of the conventional group could also be argued. A preliminary study assessed the usefulness of NIV in preoxygenation, but to our knowledge no randomized multicentre study has confirmed this hypothesis [5]. As a result, whether NIV or HFFM was the best control group remains unsure. Considering the advantages reported, the contribution of video laryngoscopy in ETI algorithm in ICU also has to be assessed [28–30]. Finally, preoxygenation quality has to be a priority area for improvement but should always be implemented in an intubation management protocol [31].

HFNC was unable to prevent desaturation but provided similar lowest saturation levels to those achieved with HFFM. Therefore, this device could be considered as a safe alternative to HFFM for preoxygenation in ICUs with specific equipment and when used by trained staff. The timing of invasive mechanical ventilation probably governs the depth of desaturation during ETI more than the preoxygenation device.

Conclusion

Despite the theoretical advantages, in acute severely hypoxemic patients, high flow nasal cannula oxygen therapy as a preoxygenation device was not more efficient than a high FiO_2 flow face mask in preventing desaturation during ETI. This study also confirms that ETI remains a landmark in a hypoxemic patient's history, with more than 50 % of severe complications.

Acknowledgments Contributors: We thank Yohann FOUCHER, EA4275 Biostatistician at Nantes University Hospital, for assistance in designing the study. We are grateful to all medical staff, nurses, and research staff at the six sites for inclusion and data collection. We thank Monique MARGUERITE for administrative and logistic support and Marion RIGOT for creating the electronic

case report form; and Dr Anne Chiffoleau, MD for safety monitoring. Financial and material support for the research and grant, funding and provision of equipment and supplies: This study was supported by the French Ministry of Health (Interregional French Clinical Hospital Research Program grant (PHRCi 2012–API12/N/077) in addition to a grant for research & innovation missions allocated to the university hospital of Nantes by Fisher & Paykel Healthcare. Nantes University Hospital sponsored the study. Fisher & Paykel participated for 14 % of the total budget including supply of consumables to the six participating centres. Fisher & Paykel did not participate in the study design or in data collection, analysis and interpretation of the data, or in the writing, review, approval and decision to submit the manuscript for publication.

Conflicts of interest Dr. Christophe Guitton and Dr. Mickael Vourc'h had full access to all of the data in the study and take complete responsibility for the integrity of the data and the accuracy of the data analysis. No conflict of interest: Mickaël Vourc'h, Christelle Volteau, Konstantinos Bachoumas, Noëmie Clavieras, Pierre-Yves Egreteau, Jean Reignier, Gwenaël Prat, Noëlle Brule, Daniel Villers, Cedric Bretonniere, Christophe Guitton. Pr Asfar received consulting fees from LFB. Pr Jaber received consulting fees from Dräger, Hamilton, Maquet and Fisher Paykel. Pr Mercat received grant support (clinical research) from Covidien, Maquet and General Electric and personal fees from Faron Pharmaceuticals (member of steering committee), Air Liquide Medical Systems and Covidien. Pr Asehnoune served as board member for Astellas, received grant support from Astellas and Pfizer; lectured for B-Braun and Fresenius. Dr Roquilly reports conflict of interest with Merck laboratory (investigator in a study).

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