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High-flow Nasal Cannulae Versus Non-invasive Ventilation for Preoxygenation of Obese Patients: The PREOPTIPOPO Randomized Trial

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A B S T R A C T

Background: In obese patients, preoxygenation with non-invasive ventilation (NIV) was reported to improve outcomes compared with facemask. In this setting, high-flow nasal cannulae (HFNC) used before and during intubation has never been studied against NIV.

Methods: The PREOPTIPOPO study is a randomised, single-centre, open-labelled, controlled trial including obese patients requiring intubation before scheduled surgery. Patients were randomised to receive preoxygenation by HFNC or NIV. HFNC was maintained throughout intubation whereas NIV was removed when apnoea occurred to perform laryngoscopy. The study was designed to assess the superiority of HFNC. The primary outcome was the lowest level of end-tidal oxygen concentration (EtO2) within 2 min after intubation. Secondary outcomes included drop in pulse oximetry and complications related to intubation.

Main findings: A total of 100 patients were randomised. The intent-to-treat analysis found median [IQR] lowest EtO2 of 76% [66–82] for HFNC and 88% [82–90] for NIV (mean difference = 12.1 [-15.1 to –8.5], p < 0.001). Mild desaturation below 95% was more frequent with HFNC (30%) than with NIV (12%) (relative risk 2.6, 95% CI 1.1 to 5.9, p = 0.03) and median lowest SpO2 during intubation was 98% [93–99] in HFNC vs. 99% [97–100] in NIV (p = 0.03). Severe and moderate complications were not different but patients reported more discomfort with NIV (28%) vs. HFNC (4%), p = 0.001.

Interpretation: Compared with NIV, preoxygenation with HFNC in obese patients provided lower EtO2 after intubation and a higher rate of desaturation <95%.

Funding: Institutional funding, additional grant from Fisher & Paykel.

Trial Registration: Clinical trial Submission: April 10, 2017.

Registry name: Preoxygenation Optimization in Obese Patients: High-flow Nasal Cannulae Oxygenation Versus Non-invasive Ventilation: A Single-centre Randomised Controlled Study. The PREOPTIPOPO Study.

ClinicalTrials.gov identifier: NCT03106441
N°ID RCB: 2017-A00305-48.

Institutional review Board: CPP Nord-Ouest I, registration number 019/2017.

URL registry: https://clinicaltrials.gov/ct2/show/NCT03106441

1. Introduction

In industrialised countries, 25% of the population is classified as obese according to the World Health Organization and may reach 50% in 2050 [1]. Difficult airway management is a daily challenge in the operating room – especially in obese patients – and gives rise to 39% of all adverse events during anaesthesia [2]. Obesity decreases the volume of functional residual capacity (FRC) of the lungs which is the main oxygen reservoir during apnoea [3], and increases the risk of intubation-related complications accordingly [4,5]. Obesity also increases the risk of difficult face mask ventilation and difficult intubation [4,6]. Desaturation during intubation appears as a major factor of morbidity given the

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Research in context

Evidence before this study

Non-invasive ventilation (NIV) used as a preoxygenation device increases the level of PaO₂ during intubation compared with a standard face mask in obese patients. Apnoeic oxygenation with nasal oxygen insufflation during intubation has been reported to delay the onset of desaturation in obese patients and continuous positive airway pressure (CPAP) during preoxygenation to prolong the non-hypoxic apnoea in the same population. As a result, in high-risk patients, 2015 international guidelines suggest preoxygenation using CPAP and recommend the administration of oxygen by nasal cannulae during intubation. Up to now, only one small sample size pilot study compared CPAP with high flow oxygen therapy by nasal cannulae (HFNC) for preoxygenation in obese patients. In that study, HFNC provided higher PaO₂ at the end of preoxygenation. Considering the increasing number of obese patients being anaesthetised every year, NIV (that combined positive end-expiratory pressure and inspiratory pressure support) and HFNC should be assessed in a larger sample size study.

Added value of this study

This is the first randomised study comparing the use of HFNC with NIV for the preoxygenation in obese patients. This study brings novel insights regarding the benefits of NIV compared with HFNC by assessing for the first time end-tidal oxygen concentration (EtO₂) after intubation which depends on four parameters: the duration of apnoea, oxygen uptake during apnoea, the volume of functional residual capacity of the lungs, and its level of oxygen saturation at the end of the preoxygenation. NIV gave rise to significantly higher EtO₂ after intubation, higher median SpO₂ during intubation and less oxygen desaturation <95%. Nevertheless, patient’s comfort during preoxygenation was better with HFNC.

Implications of all the available evidence

The PREOPTIPOP study showed that in obese patients, NIV preoxygenation provided higher EtO₂ after intubation and reduced the incidence of desaturation <95% during intubation compared with HFNC. These results also underline that EtO₂ (the usual and mandatory monitoring parameter in the operating room) after intubation is a valuable marker to predict desaturation which is an important cause of morbidity in obese patients.

difficulty of face mask ventilation for rescue oxygenation in this population. Consequently, international recommendations for anaesthetic management of the obese patients suggest to perform rapid sequence intubation (RSI) trying to minimise the time from induction to intubation [7]. RSI includes preoxygenation, immediate intubation after hypnotic administration without manual face mask ventilation.

Preoxygenation is the cornerstone of patient safety during intubation because it impacts the duration of apnoea without oxygen desaturation below a critical threshold. End-tidal oxygen concentration (EtO₂) at the end of preoxygenation is a reliable indicator of the alveolar partial pressure (PaO₂) and belongs to the gold standard of monitoring during anaesthesia in international guidelines [8]. To improve the effectiveness of preoxygenation in obese patients, the application of a continuous positive airway pressure (CPAP) or a positive end-expiratory pressure (PEEP) combined with an inspiratory pressure support (Non-invasive ventilation, NIV) were reported to enhance EtO₂ and arterial partial pressure of oxygen (PaO₂) at the end of preoxygenation, and to prolong the non-hypoxic apnoea [9–11]. However, the generation of a significant level of PEEP required an airtight face mask whose tolerance is uncertain during preoxygenation.

High-flow oxygenation by nasal cannulae (HFNC) delivers up to 60 L/min gas flow with a fraction of inspired oxygen (FiO₂) 100%. It may generate a low level of positive airway pressure and improve patient comfort compared with a face mask [12]. Contrary to face mask, HFNC makes it possible to hold nasal prongs in place after induction of general anaesthesia and during laryngoscopy trying to perform apnoeic oxygenation throughout the intubation procedure [13]. In a pilot observational study in obese patients, HFNC was found to extend apnoea time without desaturation during intubation [14].

In high-risk patients, 2015 international guidelines suggest preoxygenation using CPAP and recommend the administration of oxygen by nasal cannulae during intubation [15]. In hypoxemic critically ill patients, NIV reduced desaturation during intubation compared with HFNC (Florari 2 Study, in press Lancet respiratory medicine 2019). In obese patients, both HFNC and NIV have demonstrated advantages in the preoxygenation. Nevertheless, strong evidence is lacking to compare these two devices in the operating room. Hence, we conducted a randomised, controlled trial comparing NIV and HFNC in the preoxygenation of obese patient before intubation. The study was designed to assess the superiority of HFNC. The primary endpoint was the lowest EtO₂ within 2 min after intubation. Secondary objectives were to compare intubation complications and level of oxygen saturation measured by pulse oximetry (SpO₂) in the two groups.

2. Methods

2.1. Study Design, Setting and Ethical Consideration

The PREOPTIPOP study was a single-centre, prospective, randomised, controlled and open label trial. Patients were enrolled from June 2017 to April 2018 at Nantes University Hospital. Follow-up began when patients entered the operating room and ended on discharge from the recovery room.

Written informed consent was obtained from all patients following oral and written information received during the anaesthesia consultation. The study was approved by the institutional review board (CPP Nord-Ouest I, registration number 019/2017). The study was conducted in accordance with the Declaration of Helsinki and was registered before the first inclusion (NCT03106441). In addition to electronic data base monitoring, onsite monitoring was performed to ensure the completeness of data collection. All investigators attended a specific trial presentation and systematic training before inclusion of the first patient. Briefly, all operators performed preoxygenation and intubation sequence with the two devices for a half-day at the Nantes University Hospital simulation centre during their continuous formation program.

2.2. Participants

Eligible patients were adults with a BMI >35 kg/m² and a planned RSI airway control strategy. Exclusion criteria were: age <18 years, SpO₂ <90% in air, haemodynamic instability, patients admitted for burns, intubation without laryngoscopy (i.e. fibreoptic intubation for anticipated “cannot ventilate situation” or mouth opening <2 cm), Grade 4 glottis exposure on the Cormack-Lehane scale documented during a previous anaesthesia, adults subject to legal protection, pregnancy, lack of consent, patients without French health insurance, or already participating in an interventional study on preoxygenation.

2.3. Randomisation and Masking

Patients were randomised in an allocation ratio of 1:1 using varying different blocks sizes. The study statistician generated the allocation list.
Patients were allocated to one of the two preoxygenation strategies using a secure computer-generated online remote system controlled by the independent research promotion unit at the University Hospital of Nantes which had no role in patient recruitment. There was no masking strategy.

2.4. Intervention

The study design is described in Fig. 1. Anaesthetic management of the patients followed international guidelines [7], including anaesthesia performed by a physician accustomed to obese patients, a planned and discussed robust airway control strategy, preoxygenation in the ramped position, and drug dosing based on lean body weight.

1. Preoxygenation was performed according to the randomisation group for a four-minute period [16]. In the intervention group, preoxygenation was performed with HFNC (Optiflow™; Fisher & Paykel Healthcare, Auckland, NZ), nasal prongs set at 60 L/min flow of heated and humidified pure oxygen (FiO₂ 100%, 37 °C). In the control group, preoxygenation was performed with Face Mask (FreeMotion™ Face Mask Fisher & Paykel Healthcare, Auckland, NZ) connected to an Aisys CS² ventilation system (General Electric, GE Healthcare, Finland, Oy). In this group, ventilator was set on pressure support mode with expiratory positive airway pressure (EPAP) of 5 cm H₂O and inspiratory positive airway pressure (IPAP) of 15 cm H₂O, meaning a 10 cm H₂O pressure support, FiO₂ 100% [17].

2. Depending on patient tolerance, gas flow for HFNC or pressure support (IPAP) for NIV could be adjusted.

3. At the end of preoxygenation, RSI was performed in all patients. The use or not of neuromuscular blockers was left to the discretion of the physician owing to the lack of consensus on this point [7].

4. During laryngoscopy and intubation, HFNC was maintained in place throughout the procedure in an attempt to achieve apneic oxygenation. In the NIV group, the face mask was removed when apnea occurred in order to perform laryngoscopy. In case of difficult intubation despite external laryngeal manipulation, the stylet was the first alternative device which was proposed [15].

4. The correct position of the tracheal tube was confirmed by using capnography [18].

Standardisation of the procedure from preoxygenation until 2 min after intubation ensured reproducibility of the measure of EtO₂ (summarised in Fig. 1). Briefly, at the end of the preoxygenation procedure, all of the settings on the anaesthetic machine were adjusted to ensure that the circuit was filled with pure oxygen (FiO₂ 100%) and to avoid gas leakage out of the circuit during intubation: “bag/vent switch” set on bag, connection of a ventilator test lung and bellow on full up position. Immediately after intubation, patients were connected to mechanical ventilation (Aisys CS²) including a gas module allowing the measure the EtO₂ and the end-tidal carbon dioxide concentration (EtCO₂). The “bag/vent switch” was set on vent and assist control mode was activated, FiO₂ 100%, fresh gas flow 1 L/min, tidal volume

**Fig. 1.** Study design During preoxygenation (FiO₂ 100%), EtO₂ (Green line) increases and reflects the partial pressure of oxygen in the lung (PaO₂). During apnea, (Dotted green line) the value of EtO₂ is not available because the patient does not exhale gas. After intubation, EtO₂ decreases (Green line) to its lowest value then increases because the lung refills with FiO₂ 100% (set on ventilator, EPAP: Inspiratory positive airway pressure (cm of water), EPAP: Expiratory positive airway pressure (cm of water). EtO₂ End-tidal oxygen concentration was collected until two minutes following intubation because the measurement can be delayed by 35 s (manufacturer instructions). In order to limit measurement fluctuations, fresh gas flow was set at 1 L/min. FiO₂: Fraction of inspired oxygen, NIV: Non-invasive ventilation, HFNC: High flow oxygenation by nasal cannulae, RR: Recovery room.
6–8 mL/kg, respiration rate 15 per minute, and PEEP 5 cm H₂O. Then, 2 min following intubation, FiO₂ was set at 50% for the end of anaesthesia and inhalation anaesthetic agents were started when appropriate. This standardised procedure (setting of the anaesthesia machine and procedure to avoid gas leakage) was performed by the same external assessor for all inclusions after two days of training at the Nantes University simulation centre on a high-fidelity simulation mannequin. This allowed the attending physician to focus on preoxygenation induction and intubation.

2.5. Endpoints

To ensure the exhaustivity and the relevance of the data collection, the external assessor collected the information of the ventilator monitor for the primary and secondary outcomes. The primary endpoint was the lowest EtO₂ within the 2 min after intubation.

Secondary outcomes were: preoxygenation quality (SpO₂ at the end of the procedure) and the tolerance of the device (discomfort was considered if the patient asked for reduction of the gas flow of HFNC or the inspiratory pressure support of NIV); the process of intubation (lowest SpO₂ during intubation and within 2 min after intubation, highest level of EtCO₂ within 2 min following intubation, Intubation difficulty score (IDS) [19], Difficult intubation rate [20], desaturations below 95%, 90%, or 80%); Severe complications (death, cardiac arrest, SpO₂ <80%, systolic blood pressure <80 mmHg or vasopressor initiation) or moderate complications (ventricular or supraventricular arrhythmia requiring intervention, oesophageal intubation, vomiting with aspiration of gastric content, dental injury) related to intubation; The respiratory parameters during surgery in the hour following intubation (mean plateau and peak inspiratory pressure) were also monitored as well as the outcome in the recovery room including desaturation <90% or 80%, nausea/vomiting, or length of stay.

2.6. Sample Size

No previous study has reported EtO₂ after intubation. Based on end-preoxygenation EtO₂, we approximated the level of EtO₂ after intubation [10]. We hypothesised that HFNC would improve the mean lowest EtO₂ in the 2 min following intubation by 5% (from 78% in NIV to 83% in HFNC group) with a standard deviation of EtO₂ of 7-4%. With 90% power, a 5% type I error (two-sided tests), the required sample size was 100 patients (considering a 6% attrition rate).

2.7. Statistical Analysis

Baseline characteristics were described as count and percentage for categorical variables, mean and standard deviation or median and inter-quartile for quantitative variables when assumption of normality was not met. For primary outcome (lowest EtO₂ in the 2 min following intubation), an intent-to-treat analysis was conducted using a Wilcoxon test (unadjusted analysis). Then a linear regression model was used to account for the type of surgery (a priori planned adjusted analysis). Comparisons of secondary outcomes were performed using Chi-square tests (or Fisher tests when appropriate) for qualitative data and the Student’s t-tests (or Wilcoxon tests when appropriate) for quantitative data. No adjustment was made based on the multiplicity of tests. For qualitative data, relative risk and 95% confidence interval were estimated with the Mantel–Haenszel method. For primary outcome, a linear regression model was used to account for the type of surgery. All tests were 2-tailed. p values of less than 0.05 were considered significant. SAS software version 9.4 was used (SAS Institute Inc.). No imputation was performed because there was no missing data for the primary outcome.

2.8. Role of the Funding Source

This study was supported by institutional funds for research & innovation missions (University Hospital of Nantes) and by Fisher & Paykel Healthcare. The University Hospital of Nantes was the sponsor of the study. Nasal cannulae were loaned by Fisher & Paykel Healthcare and face masks were bought with institutional funds.

Fischer & Paykel participation was inferior to 15% of the total budget (£10,000). Fisher & Paykel did not participate in the design and the conduct of the study, nor in data collection, management, analysis and interpretation of the data, nor in the preparation, review, approval and decision to submit the manuscript for publication.

3. Results

3.1. Patients

From June 2017 to April 2018, 100 patients (N = 50 in HFNC; N = 50 in NIV) were randomised in the study. No patient withdrew consent and all of the patients were considered in the intent-to-treat (ITT) analysis (Fig. 2). At baseline (Table 1), patients were mainly middle-aged women and mostly (54%) admitted for bariatric surgery. Twenty-two (46%) patients in the HFNC and 19 (39%) in the NIV group presented obstructive sleep apnoea syndrome. Median [inter-quartile range, IQR] SpO₂ in air was 97% [97–99] in HFNC and 99% [97–100] in NIV and the mean respiratory failure risk index was 19:4 in both groups [21]. Airways, operators and technical aspects of intubation are described in Table 2. All of the patients had at least two criteria for difficult face mask ventilation. First operators were mainly junior (74% in HFNC vs. 82% in NIV). The induction of RSI combined mostly Propofol and Succinylcholine or Propofol and Remifentanil in both groups.

3.2. Primary Outcome: The Lowest EtO₂ in the 2 min Following Intubation

In the intent-to-treat (ITT) analysis (Table 3), the lowest EtO₂ within the 2 min after intubation was significantly higher in NIV than in HFNC group, 88% [82–90] vs. 76% [66–82] respectively, (mean difference −11 · 4 [7·7 to 15·1], p = 0·0001) (Fig. 3). Although intubation was performed for planned surgery, the lowest EtO₂ ranged from 53% to 94% in the NIV group and from 37% to 87% in the HFNC group. A priori planned adjusted analysis to the type of surgery confirmed the significant improvement of the primary endpoint in NIV group (mean difference 12·1 [8·5 to 15·1], p < 0·0001). An exploratory subgroup analysis studying the bariatric surgery subgroup of patients also found a higher EtO₂ in NIV vs. HFNC group with a mean EtO₂ difference of 11·3 [5·5 to 17·2], p = 0·003.

3.3. Secondary Outcomes

All randomised patients underwent 4-min preoxygenation. Patients in the NIV group reported significantly more discomfort requiring a reduction of pressure support compared with patients in the HFNC group (reduction of air flow), respectively 14 patients (28%) vs. 2 patients (4%) (relative risk 0·1, IC 95% [0·03 to 0·6], p = 0·01). No patient interrupted NIV or HFNC during the preoxygenation. Consistently with EtO₂ differences, median [IQR] lowest SpO₂ during intubation and the two following minutes were significantly improved with NIV compared, respectively 99% [97–100] vs. 98% [93–99], p = 0·03. In the same way, 15 patients (30%) in the HFNC group vs. 6 patients (12%) in the NIV group experienced a drop of SpO₂ below 95% (relative risk 2·5, IC 95% [1·1 to 5·9], p = 0·001). We also confirmed that patients who presented oxygen desaturation <95% had lower median [IQR] EtO₂ after intubation vs. patients who did not: 66 [63–78] vs. 84 [77–88], p < 0·0001. At the end of intubation, the highest level of EtCO₂ was not different with HFNC compared with NIV, respectively 4·2 [3·5–4·8] vs. 3·9 [3·3–4·4], p = 0·09. The rate of difficult
intubation, and IDS score were not different between the two groups. Severe and moderate complications occurred respectively in 4 (8%) patients in HFNC vs. 6 (12%) in NIV, (p = 0.99), and 1 (2%) in HFNC vs. 1 (2%) in NIV, (p = 0.99). During surgery, there was no difference between HFNC and NIV regarding the mean plateau and peak inspiratory pressures. In the recovery room, the length of stay, the rate of nausea/vomiting and desaturation below 90% or 80% were not different in the two groups either. Finally, the rate of planned admissions to the ICU after surgery for sleep apnoea syndrome or chronic heart failure were similar in the two groups, respectively 21 patients (42%) in the HFNC group and 19 patients (38%) in the NIV group (p = 0.53). No patient required unplanned admission to the ICU.

4. Discussion

This trial was designed to test the superiority of HFNC over NIV. On the contrary, NIV significantly improved the lowest EtO₂ within 2 min after intubation compared with HFNC. NIV consistently gave rise to a higher level of SpO₂ during intubation and decreased by 2.5-fold oxygen desaturation <95%. Intubation related complications and post-operative outcome were not different in the two groups. These results must be tempered by a 7-fold increase in discomfort in patients receiving NIV compared with HFNC. Despite scheduled surgery, pre-

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**Fig. 2. Study flow chart HFNC: High-flow nasal cannulae, NIV: Non-invasive ventilation, ITT: Intent-to-treat analysis, SpO₂: Level of oxygen saturation measured by pulse oximetry.**

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**Table 1**
Baseline characteristics of the intent-to-treat population.

|                        | High-flow nasal cannulae | Non-invasive ventilation |
|------------------------|--------------------------|--------------------------|
| **Gender ratio M/F**   | 16/34                    | 14/36                    |
| **Age, median [IQR], y** | 51 [43-60]             | 46 [32-55]              |
| **BMI, mean (SD)**     | 42 (5)                   | 41 (4)                   |
| **Type of surgery, n (%)** |                        |                          |
| Bariatric              | 24 (48%)                 | 30 (60%)                 |
| Digestive-non-bariatric| 12 (24%)                 | 12 (24%)                 |
| Orthopaedic            | 4 (8%)                   | 1 (2%)                   |
| Head and Neck          | 0                        | 0                        |
| Urologic               | 4 (8%)                   | 5 (10%)                  |
| Plastic                | 6 (12%)                  | 2 (4%)                   |
| **Comorbidities n (%)** |                        |                          |
| McCabe scale 1b        | 47 (94%)                 | 45 (90%)                 |
| Chronic heart failure  | 1 (2%)                   | 0 (0%)                   |
| High blood pressure    | 24 (48%)                 | 21 (42%)                 |
| COPD                   | 3 (6%)                   | 2 (4%)                   |
| Obstructive sleep apnoea| 22 (46%)              | 19 (39%)                 |
| Active smoking         | 16 (32%)                 | 9 (18%)                  |
| Diabetes               | 7 (14%)                  | 3 (6%)                   |
| Past upper airway tract cancer | 0           | 0                        |
| Cirrhosis              | 0                        | 1 (2%)                   |
| SpO₂ in air, median [IQR], % | 97 [97-99]           | 99 [97-100]             |
| Respiratory failure risk index, mean (SD)
| 19.4 (8-7)             | 19.4 (6-9)              |

**Table 2**
Airway and intubation setting at baseline.

|                        | High-flow nasal cannulae | Non-invasive ventilation |
|------------------------|--------------------------|--------------------------|
| **Airway description, n (%)** |                      |                          |
| At least 2 difficult mask | 50 (100%)              | 50 (100%)                |
| ventilation criteriaa  | 3 (6%)                   | 1 (2%)                   |
| History of difficult intubation | 3 (6%)              | 1 (2%)                   |
| Mouth opening less than 3 cm | 2 (4%)                  | 2 (4%)                   |
| Thyroid bone to chin distance <65 mm | 1 (2%)              | 0 (0%)                   |
| Limination of cervical mobility ≤35 degrees | 1 (2%)              | 5 (10%)                  |
| Mallampati III or IV    | 14 (28%)                 | 10 (20%)                 |
| Intubation, n (%)       | 37 (74%)                 | 41 (82%)                 |
| First operator, juniorb | 50 (100%)               | 49 (98%)                 |
| Drug for anaesthesia    | 0                        | 2 (4%)                   |
| Propofol                | 25 (50%)                 | 33 (66%)                 |
| Etomidate               | 6 (12%)                  | 3 (6%)                   |
| Neuromuscular blocking agent |                      |                          |
| Succinylcholine         | 23 (46%)                 | 15 (30%)                 |
| Rocuronium              | 2 (4%)                   | 2 (4%)                   |
| None                    | 25 (50%)                 | 33 (66%)                 |

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a Age > 55 years, BMI > 26, thyroid bone-to-chin distance <60 mm, snoring, beard, lack of teeth, limitation of mandibular protrusion.

b Residents were considered as junior operators. Doctors of medicine were considered as seniors.
anaesthesia assessment, and trained medical staff, severe complications occurred in 10% of the patients, 9% experienced SpO₂ < 90%, and 11% required two operators or more to perform intubation.

The present study confirms that NIV is a relevant device for the preoxygenation of obese patients [9–11]. Conversely, HFNC was previously reported to lead to higher PaO₂ during preoxygenation in obese patients compared with 7 cm H₂O continuous positive airway pressure (CPAP) or face mask [22]. Interestingly, apnoeic oxygenation by continuous administration of low-flow oxygen by nasal prongs during intubation was reported to prevent desaturation in the same population [23]. In the present study, HFNC brought lower EtO₂, lower SpO₂ and more oxygen desaturation than NIV. These discrepancies with previous studies could be explained by their small sample and quasi experimental design and the lack of inspiratory pressure support combined with positive airway pressure in Heinrich et al. study [22]. Moreover, achieving effective apnoeic oxygenation requires 1) airway patency during apnoea and 2) a preserved FRC. For the first point, the limited supra-glottic positive pressure generated by HFNC was probably unable to remedy airway obstruction after general anaesthesia [12]. For the second point, the low level of positive pressure generated by HFNC could be unable to maintain or restore the impairment of FRC in obese patients [24]. Nevertheless, given its better tolerance and the high median SpO₂ during intubation in both groups, HFNC is an acceptable alternative device in obese patients when NIV is not available or contraindicated. In NIV group, patients mainly complained for too high level of inspiratory support which provoked coughing. To improve the tolerance, gradual increase of inspiratory support could be an option so as not to exceed a pre-specified and secure tidal volume. The theoretical risk of gastric insufflation previously reported using NIV did not increase the occurrence of aspiration or nausea and vomiting in the recovery room compared with HFNC in this study. Two patients in the HFNC group reported sinus pressure during preoxygenation which was corrected by decreasing the flow rate.

One of the main challenges of anaesthesia in obese patients is therefore to quickly proceed to intubation after the induction of anaesthesia. Otherwise, oxygen desaturation can occur and require mask ventilation for rescue oxygenation which is often difficult and sometimes impossible – thereby leading to severe adverse events such as gastric insufflation, aspiration, severe desaturation and associated haemodynamic instability, or cardiac arrest [25]. As soon as the level of pulse oximetry drops below 95% during intubation, current guidelines advise interrupting intubation to focus on oxygenation (i.e. face mask ventilation) [26]. In the present study, we observed a 2-fold reduction of the occurrence of SpO₂ < 95% in the NIV group compared the HFNC group which is a major finding given the issues regarding face mask ventilation in this population.

This trial has several limitations. The small size of the sample and the single-centre design may have overestimated the effect of treatment.
and could limit generalisation of the results [27]. However, the management of obese patients is broadly standardised in the operating room and the protocol adhered to international anaesthetic guidelines [7]. Patients were 5 years older at baseline in HFNC group which could have biased assessment. The first operators were mainly junior and had received specific training for the two devices in a simulation centre. They were supervised by a senior physician who was accustomed to obese patients. These prerequisites enhanced the external validity of the results vis-à-vis the daily practice in the operating room. Lastly, the mean BMI of 40 enabled generalisation of the results to severely obese patients. The unblinded preoxygenation device may have interfered with the results. Although feasible, blinding would have required the association of the two devices which could have reduced the ability of NIV to generate positive end-expiratory pressure owing to incomplete air tightness [13]. The measurement of Eto2 can be biased which is the reason ventilator settings were optimised according to manufacturer guidelines in order to obtain a standardised, reproducible and reliable value of Eto2. Eto2 is not available during apnoea because it requires an expired gas flow. Usually, after connection to the ventilator, FiO2 100% is maintained until the confirmation of the correct position of the tracheal tube. In order to reduce bias while measuring Eto2, the use of 1 L/min fresh gas-flow limits the risk of entrained pure oxygen from the inspiratory branch of the circuit. For the same reason, the operator should avoid using gas bypass. In addition, in order not to entrain room air and avoid gas leaks, the operator has to ensure that circuit is closed during (ventilator test lung) and after intubation (balloon cuff inflated). After connection to the ventilator, Eto2 decreases down to the nadir and then slowly rises again up to a value which is near from the FiO2. That’s why the measure should be done early following intubation. Finally, in patients with increased dead space, the measure remains reliable but Eto2 > 90% may be harder to reach at the end of preoxygenation. All the patients underwent RSI in order to ensure that manual face mask ventilation before intubation does not interfere with the primary outcome. Patients received either neuromuscular blocker or high dose remifentanil (2–3 micrograms/kg) leading both to prompt apnea and providing with acceptable intubating conditions [28,29]. As a result, no patient was spontaneously breathing throughout the intubation. The low rate of severe desaturation <80% may be explained by the inclusion of non-hypoxemic patients undergoing non-urgent surgery in the light of our previous results [30].

Eto2 after intubation as the primary endpoint had never been addressed up to now and its interest should be discussed. Eto2 is a mandatory standard of monitoring during all anaesthesia. Neither SpO2 nor Eto2 after intubation are as accurate as PaO2 in a blood gas sample [31]. Nevertheless, systematic arterial catheterisation could not be ethically argued for scheduled non-haemorrhagic surgery. SpO2 and Eto2 after intubation both provide complementary information: as described above, SpO2 is used as a warning to help the operator to decide when to stop the procedure and to proceed to rescue oxygenation. Contrary to end-preoxygenation Eto2 (which only depends on PAO2), Eto2 after intubation depends on oxygen uptake during apnoea, duration of apnoea, and the total amount of oxygen available in the lung at the end of preoxygenation (results from multiplying the volume of FRC and PAO2). Consequently, for comparable median duration of apnoea and assumed similar oxygen uptake in this randomised study, higher Eto2 after intubation suggests that NIV stocks a higher amount of oxygen than HFNC during preoxygenation. One could hypothesise that both the ability of inspiratory pressure support to increase PAO2 and PEEP to maintain, restore or increase FRC during preoxygenation could account for these results [29–31]. Moreover, the lower Eto2 in HFNC suggests that attempting apnoeic oxygenation by holding the device in place throughout the procedure did not offset oxygen uptake during apnoea. The relative effects of preoxygenation with NIV or HFNC on patient-centered outcomes remains unclear. Nevertheless, these results show that Eto2 after intubation is clinically relevant to assess patient safety: Its decrease is an indicator of the reduction of the amount of oxygen available to ensure oxygenation during apnoea and thus, an early surrogate marker of desaturation. Moreover, Eto2 appears as a new tool to discriminate between preoxygenation devices that would provide slightly different median SpO2 during intubation (i.e. in the present study 98% [93–99] in HFNC vs. 99% [97–100] in HFFM). In this setting, the oxygen reserve index (ORI) will have to be assessed as well [32]. It could stand as an interesting tool to differentiate two preoxygenation devices leading to similar SpO2. This non-dimensional index that ranges from 1 to 0 will have to be compared to one of the references, either PAO2 or PaO2 and its clinical applications will have to be determined during intubation.

5. Conclusion

The PREOPTIPPO study showed that NIV as a preoxygenation device gives rise to higher Eto2 within the 2 min after intubation, higher median level of pulse oximetry, and less desaturation <95% during intubation compared with HFNC. Nevertheless, patients reported better tolerance with HFNC than with NIV. Eto2 after intubation appears to be a valuable tool to differentiate two preoxygenation devices.

Author Contributions

Pr. Karim Asehnoune and Dr. Mickael Vourc’h had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Study concept and design: Dr. Mickael Vourc’h, Pr. Karim Asehnoune, Pr. Samir Jaber, Dr. Christophe Guitton and Dr. Gabrielle Baud.

Data acquisition: Dr. Mickael Vourc’h, Pr. Karim Asehnoune, Dr. Gabrielle Baud, Claire Blanchard and Pr. Eric Mirallie.

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Drafting of the manuscript: All of the authors.
Critical revision of the manuscript for important intellectual content: All of the authors.

Editing the manuscript: Peter Tucker, a native English speaker, edited the manuscript.

Statistical analysis: Fanny Feuillet.

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Study supervision: Dr. Mickael Vourc’h and Pr. Karim Asehnoune.

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Collaborators and Additional Contributions

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Data Sharing Statements

De-identified data collected for the study, including individual participant data and a data dictionary defining each field in the set will be made available to others. Statistical analysis plan, informed consent form and full dataset will be made available on reasonable request by addressing an email to the corresponding author within five years following publication with investigator support.

Declaration of Competing Interest

Fanny Feuillet, Claire Blanchard, Eric Miraille and Christophe Guitton declare no conflict of interest. Mickael Vourc’h declares personal fees from MSD, Pfizer, Baxter and grants from Fischer Paykel, outside the submitted work. Samir Jaber reports personal fees from Draeger, Fresenius-Xenios and Fisher Paykel Healthcare, outside the submitted work. Karim Asehnoune declares personal fees from Fisher Paykel Healthcare, Baxter, LFB, Fresenius.

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