Acute Respiratory Failure after Cardiothoracic Surgery: Noninvasive Ventilation

(BiPAP) versus OPTIFLOW™

Multicenter, randomized, noninferiority trial (BiPOP study)

Usual care: both devices are widely used.

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CURRENT KNOWLEDGE

Respiratory changes after cardiothoracic surgery include changes in breathing pattern, increased work of breathing, a restrictive ventilatory defect, hypoxemia, and respiratory muscle dysfunction (1, 2). These changes can persist for 6 to 8 weeks.

Respiration is a complex activity that requires the coordinated involvement of several muscle groups located in the upper airways and rib cage. In some patients, respiratory muscle dysfunction in the perioperative period may be related chiefly to impaired coordination, as opposed to loss of global muscle activity (2). The work of breathing is increased nearly 2-fold in the immediate postoperative period (3). The effects of thoracic surgery on respiratory function result from three main mechanisms: incision of the intercostal muscles, postoperative pain, and diaphragmatic dysfunction occurring as a reflex response to visceral stimulation (2).

Diaphragmatic dysfunction may result from supradiaphragmatic stimuli that require compensatory rib-cage involvement (4). In patients undergoing elective lung resection, shortening of the costal diaphragm was decreased during the first few hours after surgery, an impairment that was not improved by thoracic epidural lidocaine anesthesia (4). A study reported in 2000 established that pain contributed to inspiratory muscle dysfunction after upper abdominal surgery (5).

Other factors that may participate in the development of pulmonary complications include bronchoconstriction induced by endotracheal intubation and/or medications, impaired mucociliary function, and substances released by cells involved in pulmonary inflammation (2).

These respiratory function changes, most notably the hypoxemia, are associated with postoperative morbidity. Several noninvasive interventions are available to minimize them.
Effective respiratory physiotherapy is mandatory in all patients. Among other tools for improving respiratory function and oxygenation, the most important are nasal-prong or facemask oxygen therapy; noninvasive ventilation (NIV); and a more recently introduced treatment, namely, high-flow nasal oxygen therapy (HFNO).

**NONINVASIVE VENTILATION (NIV)**

The term “NIV” encompasses all the ventilatory assistance methods that produce all or part of the work of breathing without requiring endotracheal intubation, the goal being to ensure sufficient alveolar ventilation. At present, bi-level positive airway pressure ventilation (BiPAP) is by far the most widely used NIV modality.

**Practical aspects of noninvasive ventilation (NIV)**

NIV is used intermittently over the 24-hour period. Choices must be made regarding the interface (nasal or full-face mask), ventilatory mode, and ventilatory settings. In addition to potentially avoiding endotracheal intubation and the attendant complications, NIV has many technical advantages: numerous parameters can be adjusted to achieve individual patient tailoring (e.g., interface, time used per 24 hours, and ventilatory mode); the patient can speak, eat, and take oral medications; physiological cough mechanisms are preserved and even enhanced by the mechanical insufflation; mobilization of the patient is facilitated; deep sedation is unnecessary; and the intermittent application schedule ensures weaning at the earliest possible time.

However, NIV is also associated with complications and drawbacks (6). Active patient cooperation is required, and the workload for the ICU staff is often greater than with endotracheal ventilation. Other problems include poor tolerance of the interface; air leaks
that severely compromise the effectiveness of NIV; and prolonged apneas, particularly with
the pressure-support mode. NIV may be difficult to apply in patients who have a nasogastric
tube or altered chest-wall compliance. The success of NIV depends to a substantial extent on
the motivation and experience of the physicians and other healthcare workers in charge of
the patient. Close monitoring in appropriate surroundings is mandatory to ensure that
endotracheal intubation is performed promptly if needed.

NIV and postoperative respiratory failure

Several publications have reported the effects of NIV (continuous positive airway
pressure [CPAP] and BiPAP) on postoperative ventilatory function. In most of the studies,
the patients underwent scheduled surgery and did not have acute respiratory failure. In this
population, NIV had relatively favorable outcomes, particularly in terms of gas exchange
and pulmonary volumes, but these benefits were often short-lived. Early studies usually
compared CPAP with standard care (oxygen plus physiotherapy) and showed improvements
in oxygenation and several ventilatory parameters. Among these studies, only one (7) found
that NIV (usually CPAP) was associated with a decreased incidence of atelectasis.

A randomized trial in 96 patients undergoing coronary artery bypass grafting with
mammary arteries evaluated whether CPAP or BiPAP during the first 2 postoperative days
was effective in preventing lung function deterioration (8). CPAP at 5 cm H₂O was provided
for 1 hour every 3 hours. BiPAP was also given for 1 hour every 3 hours, with a mean
positive-support ventilation level of 12 cm H₂O and a mean positive end-expiratory pressure
(PEEP) of 5 cm H₂O. The control condition was incentive spirometry for 20 minutes every 2
hours. Using both CPAP and BiPAP significantly improved oxygenation, vital capacity (VC)
and forced expiratory volume in 1 second (FEV1). However, the frequency of atelectasis
was similar in the three groups (12%-15%) (8). Sound evidence demonstrates that NIV is
beneficial, most notably in improving gas exchange and ventilatory parameters, without inducing deleterious hemodynamic effects.

In a physiologic study, the effects of a 1-hour trial of NIV (BiPAP) after elective pulmonary resection were assessed in 10 patients, who were compared to 9 controls (9). No NIV-related complications were recorded. NIV improved oxygenation without increasing leaks around the chest drains. An observational study collected data on the effects of NIV in 21 patients with acute respiratory failure after bilateral lung transplantation (10). All patients tolerated NIV well, and NIV obviated the need for re-intubation in 18 patients.

A randomized trial established that NIV was effective in patients with acute respiratory failure after lung resection (11). Each group had 24 patients. NIV delivered via a nasal mask using a single-circuit ventilator was compared with standard care (oxygen plus physiotherapy plus bronchodilators). Invasive mechanical ventilation was required in only 21% of the NIV-treated patients, compared to 50% of the controls; mortality in these two groups was 13% and 38%, respectively. Oxygenation improved starting at the second hour of NIV with 9 cmH₂O of pressure support and 4 cmH₂O of PEEP. To date, this is the only randomized trial demonstrating that NIV decreases the frequencies of intubation and death in patients with acute respiratory failure after thoracic surgery (11).

However, in a retrospective study, 40 (29.6%) of 135 patients who received NIV after lung resection or pulmonary endarterectomy eventually required invasive mechanical ventilation (12). Four variables were independently associated with NIV failure during the first 48 hours: higher respiratory rate (OR, 4.17 [1.63-10.67], higher SOFA score (OR, 3.05 [1.12-8.34], higher number of fiberoptic bronchoscopies (OR, 1.60 [1.01-2.54], and higher number of hours on NIV (OR, 1.06 [1.01-1.11]).

High-flow nasal oxygen therapy (HFNO): the OPTIFLOW™ device
The administration of humidified HFNO via a nasal cannula (OPTIFLOW™) may have several advantages over low-flow oxygen therapy. HFNO may result in higher FiO₂ values compared to high-flow facemask oxygen therapy (13). The high flow of gas decreases the dilution of oxygen in the environmental air (14), and the continuous flow ensures washout of the nasopharyngeal dead space (15). Nasal interfaces are generally well tolerated by patients, who also benefit from a high level of humidity (16).

Even in patients who prefer nasal interfaces, the lack of humidification with conventional nasal prongs precludes the delivery of oxygen flows greater than 4 to 6 liters/minute. With HFNO, the high level of humidification and unique nasal interface result in good patient comfort. The nasal interface fits comfortably despite the wide interindividual variability in nasal morphology. It is effective in delivering continuous high flows without gas spurts.

OPTIFLOW™ delivers up to 50 L/min of gas heated at 37°C and humidified at 44 mgH₂O/L (i.e., at body temperature and pressure saturated [BTPS]). BTPS-conditioned gas inspired through the nose is nearly imperceptible even when delivered at high flow rates (17).

Although many masks are available for high-flow oxygen therapy, most of them deliver FiO₂ values no greater than 50%, with or without humidification. The few studies of HFNO suggest better efficacy compared to high-flow facemask oxygen. A cross-over comparison of a nasal cannula versus the Hudson facemask for delivering humidified high-flow (15 L/min) oxygen after elective termination of pregnancy showed considerably higher values of expired end-tidal O₂ fraction (FETO₂) with nasal administration (15). A study that relied on a model of the upper respiratory tract demonstrated higher FiO₂ values when delivering oxygen via high-flow nasal prongs rather than via a facemask (13). In both studies (13) (15), the authors pointed out that the continuous flow of gas ensured complete
elimination of the expired gas from the upper airway, thereby decreasing the anatomic dead space.

Gas inflow and outflow vary during the respiratory cycle. During inspiration, gas inflow peaks at about 30-40 L/min (17). When the supplemental oxygen flow is below the peak inspiratory flow, room air is inspired also. High-flow gas therapy may minimize this air dilution in patients with high tidal volume and peak inspiratory pressure values (14).

High-flow oxygen therapy via a facemask may be poorly tolerated by patients with claustrophobia. In patients who cannot tolerate a facemask, adequate PaO₂ values cannot be achieved using NIV; if no other option is available, mechanical ventilation must be used, resulting in greater patient discomfort, morbidity, and healthcare costs (18). A study of heated humidified air delivery during sleep in patients with xerostomia due to Sjögren’s syndrome who had failed to tolerate humidified facemask therapy reported good tolerance of the OPTIFLOW™ device (19). At the end of the study, 50% of the patients said they wanted to continue OPTIFLOW™ treatment at home.

Benefits of humidification

Contrary to conventional oxygen therapy, the administration of humidified heated gas at BTPS directly into the nostrils prevents cooling and dryness of the airways. High-flow oxygen therapy has been associated with decreased ciliary activity and compromised mucociliary clearance. Optimal humidification may contribute to maintain effective clearance of airway secretions (21).

In patients with acute respiratory failure who receive oxygen via a facemask, cooling of the airways may induce reflex bronchoconstriction. A study of patients with stable advanced chronic obstructive pulmonary disease (COPD) showed that HFNO via OPTIFLOW™ decreased dyspnea and improved oxygenation compared to low-flow oxygen
therapy (22). The suggested underlying mechanisms were decreased room-air entrainment and the preventive effect of humidity against an increase in airway resistance. \( \text{FiO}_2 \) measurements at oxygen flows of 6, 8, and 10 L/min delivered via nasal prongs showed similar or higher values with the mouth open compared to closed (23). Higher \( \text{FiO}_2 \) values during mouth-open breathing were also noted in healthy volunteers during low-flow and high-flow nasal oxygen delivery (24).

Two studies demonstrated a decrease in breathing rate with HFNO (15, 22). A dead-space reduction may explain this effect. In adults, some degree of positive pressure is generated at the end of expiration. In two other studies, HFNO therapy generated PEEP, which correlated with the flow rate, ranging from 3 cmH\(_2\)O at 20-35 L/min to 7 cmH\(_2\)O at 60 L/min (25, 26). Intratracheal pressure has also been shown to increase with gas flow (22).

In sum, HFNO therapy via OPTIFLOW™ decreased oxygen dilution in room air (14-16, 22) and diminished the dead space (15, 16). The administration of heated and humidified gas preserved the clearance of airway secretions and decreased the occurrence of reflex bronchoconstriction (21). Finally, HFNO therapy induced PEEP, whose level was proportional to the oxygen flow rate (25, 26).

**OPTIFLOW™ in postoperative respiratory failure**

The OPTIFLOW™ device has been evaluated in 10 patients with advanced COPD (22) and 60 patients after cardiothoracic surgery (27). In this last study (27), rescue NIV rates were lower and desaturation episodes less common in patients treated with OPTIFLOW™ compared to standard oxygen therapy. Recently, the device has shown promise in ICU patients with respiratory failure (28). A systematic review of 8 studies in adults admitted to the ICU with acute respiratory failure indicated that OPTIFLOW™ therapy improved oxygenation, decreased work of breathing, and increased airway pressures (29). Oxygenation
improved significantly, due to a better match between the patient’s inspiratory flow and the delivered oxygen flow (up to 60 L/min) compared to high-flow mask therapy, and possibly also to the induction of some degree of PEEP (29). Regarding the PEEP effect a 1:1 randomized trial in 150 post-cardiac surgery patients with radiological atelectasis scores ≥2 compared routine CPAP (5 cmH2O, four 30-minute sessions per day) to routine NIV (10 cmH2O pressure support and 5 cmH2O PEEP) (30). The proportion of patients whose radiological atelectasis score improved was significantly greater in the NIV group than in the CPAP group. A crossover study of oxygen therapy for acute respiratory failure showed greater patient comfort with OPTIFLOW™ than with a facemask (31). Other benefits of OPTIFLOW™ therapy included significantly improved oxygenation and lower breathing rates (31).

In conclusion, OPTIFLOW™ is being increasingly used to treat acute respiratory failure, based on reports of a number of benefits. However, criteria for choosing between OPTIFLOW™ therapy and BiPAP NIV remain unclear. A study comparing OPTIFLOW™ therapy to BiPAP NIV in the immediate postoperative period should help to define the role for each method, thereby improving the management of patients with postoperative acute respiratory failure.
REFERENCES


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28- Sztrymf B, Mayot T, Dreyfuss D, Ricard JD. Intérêt de l'oxygenothérapie à haut débit humidifiée (Optiflow®) en réanimation: premiers résultats. SRLF 2010
29- Kernick J, Magarey J. What is the evidence for the use of high flow nasal cannula oxygen in adult patients admitted to critical care units? A systematic review. Aust Crit Care 2010; 23: 53-70.


The primary objective is to determine whether OPTIFLOW™ HFNO therapy is not inferior to NIV (BiPAP Vision®) after cardiothoracic surgery, in patients with either immediate postoperative acute respiratory failure (ARF) or a high risk of ARF immediately after extubation. The primary outcome is the failure rate, with failure defined as a need to reintubate, a need to switch to the other study treatment, or patient refusal to continue the randomly allocated study treatment.

The secondary outcomes are as follows:

- dyspnea score changes over time,
- skin breakdown and patient comfort,
- changes over time in the respiratory and hemodynamic variables,
- number of fiberoptic bronchoscopies during the ICU stay,
- number of episodes of postoperative pneumonia and consumption of antibiotics, and
- ICU and hospital stay durations.

PATIENTS AND METHODS

Study design

Prospective, single-center, interventional, open, randomized trial in two parallel groups of post-cardiothoracic surgery patients, treated with either bi-level positive airway pressure (BiPAP) noninvasive ventilation (NIV) or high-flow nasal oxygen (HFNO) via the OPTIFLOW™ device. The study is expected to last about 2 years.

Patients
(1) Inclusion criteria

Patients were eligible immediately after cardiothoracic surgery in two situations.

- Postextubation ARF, defined as at least one of the following:
  
  - partial pressure of arterial oxygen (PaO\textsubscript{2})/fraction of inspired O\textsubscript{2} (FiO\textsubscript{2}) less than 300,
  
  - respiratory rate greater than 25/minute for at least 2 hours,
  
  - use of accessory respiratory muscles, and
  
  - paradoxical respiration.

- High risk of postextubation ARF defined as at least one of the following:
  
  - arterial O\textsubscript{2} saturation (SaO\textsubscript{2}) less than 90% with 12 L of O\textsubscript{2} during a T-tube trial,
  
  - PaO\textsubscript{2} less than 75 mmHg with an FiO\textsubscript{2} of at least 0.5 during low-level pressure support,

  - one or more of the following risk factors,
    
    - body mass index >30 Kg/m\textsuperscript{2}
    
    - left ventricular ejection fraction <40%
    
    - failure of previous extubation, and
    
    - stridor

(2) Exclusion criteria

Exclusion criteria were as follows:

- history of obstructive sleep apnea syndrome,

- tracheostomy,

- coma not related to hypercapnia,

- bradypnea,

- cardiac arrest,
• history of recent gastric surgery,
• agitation and/or poor cooperation,
• nausea and/or vomiting, and
• hemodynamic instability.

Sample size estimate

Hypothesis

In patients in the postoperative period after surgery for lung disease, heart disease, or chronic thromboembolic pulmonary hypertension, OPTIFLOW™ treatment is not inferior to NIV via a facemask (BIPAP Vision®)

Primary outcome

The primary outcome was the rate of failure of OPTIFLOW™ treatment versus BiPAP Vision® treatment for postoperative hypoxia after surgery for lung disease, heart disease, or chronic thromboembolic pulmonary hypertension. According to the above-stated hypothesis, we expected that this failure rate would not be higher with OPTIFLOW™ compared to BiPAP Vision®. The definition of “failure” used for this study is given below.

Feasibility

We expected that about 500 patients would be eligible at our center each year.

Assessment criteria

• Primary outcome

The primary outcome was study-treatment failure defined as any of the following: need to reintubate, need to switch to the other study treatment, and patient refusal to continue the randomly allocated study treatment.

• Secondary outcomes

  o dyspnea score changes over time,
o skin breakdown and patient comfort,
o changes over time in the respiratory and hemodynamic variables,
o number of fiberoptic bronchoscopies during the ICU stay,
o number of episodes of postoperative pneumonia and consumption of antibiotics, and
o ICU and hospital stay durations.

Sample size

- Assumptions: for this comparison of two groups, with $\alpha$ set at 0.05 and $\beta$ at 0.20 (80% power), the expected failure rate was 20% with NIV (P2) and 22%-25% with OPTIFLOW™ (P1.1); the noninferiority margin $\delta$ was set at 5%-9% (D0) and the expected loss-to-follow-up rate was 0%.

- Sample size calculation

Noninferiority would be established if the upper limit of the one-sided 95% confidence interval for the between-group difference in treatment failure rates was less than 9%, with $\alpha$ set at 0.05. Assuming failure rates of 20% in the BiPAP group and 22% in the OPTIFLOW™ group (i.e., a maximal failure rate of 29% to accept noninferiority), to obtain 80% power for establishing noninferiority of OPTIFLOW™ compared to BiPAP, 838 participants were required.

Because statistical power may diminish considerably if the primary outcome is achieved less often than expected, an interim analysis will be conducted after inclusion of the first 400 patients, to re-assess the validity of the sample size estimate. This interim analysis will neither assess the difference between the two treatments nor modify the $\alpha$ risk.

Conduct of the study (Figure)
Patients will be selected based on the above-listed criteria. The investigator providing care to the patient will check that all inclusion criteria are present and all exclusion criteria are absent. The investigator will provide the patient with oral information on the study objectives and on the conduct of the study, both orally and by handing the patient a printed information document. After allowing the patient sufficient time to make a decision, the investigator will ask the patient to sign a printed informed-consent document.

Randomization in a 1:1 ratio will be performed in blocks of 2, 4, or 6 patients to ensure that the number of patients in each group is the same in each study center. There will be a single randomization sequence for all centers, generated using nQuery Advisor® software.

Concealment will be achieved by using opaque sealed envelopes. A log of all eligible patients indicating which patients were included and which were not included will be kept at each study center. We will use these logs to determine the proportion of eligible patients who were included and to compare the characteristics of included and nonincluded eligible patients.
Figure

Post-cardiothoracic surgery patients

Eligible patients

Not included

INFORMATION AND CONSENT

RANDOMIZATION

OPTIFLOW™

NIV BiPAP Vision®

SUCCESS/FAILURE
Methods

1) Settings for initiating OPTIFLOW™:
- Flow rate 50 L·min⁻¹
- FiO₂ to achieve SaO₂ ≥92%
- Continuous treatment around the clock

2) NIV
- The first session will last at least 2 hours.
- Subsequently, NIV will be applied for at least 1 hour every 4 hours. NIV duration will be increased if needed to achieve clinical respiratory stability.
- Pressure support will be 8 cmH₂O initially and will be adjusted subsequently to achieve an exhaled tidal volume of 8 mL·Kg⁻¹ and a respiratory rate lower than 25 breaths·min⁻¹. PEEP will be set initially at 4 cm H₂O.

3) Criteria for stopping OPTIFLOW™ and NIV
In the OPTIFLOW™ group, during each morning round, OPTIFLOW™ therapy will be stopped and medium-flow O₂ given instead, via nasal prongs or a facemask.
OPTIFLOW™ therapy will not be restarted if PaO₂/FiO₂ remains >300 and/or SaO₂ ≥95%.
NIV will be stopped if required for less than 4 hours/day.

Materials
For NIV, we will use the BiPAP® Vision (Respironics®, Respironics France, 44475 Carquefou, France), a positive pressure-controlled ventilator operated by a microprocessor.
Features of this ventilator include a user interface with multi-function keys, an integrated display screen that shows real-time graphics, and integrated patient and system alarms. All the functions of the system are checked when the device is turned on then during operation of the device. Pressure control is achieved by monitoring proximal airway pressure and adjusting the airflow to ensure that this pressure stays at the predefined target.
The ventilator will be used with the accessories provided by Respironics, namely, the PerformaTrak kit (Ref. 1019524) with the PerformaTrak facemask (Ref. 1012573) available in three sizes (small, medium, and large); an antibacterial filter (Ref. 1014047, with a low resistance of 0.7 cmH₂O at 0.5 L/s and 68 mL of static dead space); and a single-branch patient circuit with an integrated calibrated intentional leak, Ref. 582072).

The OPTIFLOW™ device will be provided by Fisher & Paykel Healthcare France (91946 Courtaboeuf, France). This device delivers up to 50 L/min of gas at BTPS (i.e., heated at 37°C and humidified at 44 mg H₂O/L). The nasal cannulas will also be provided by Fisher & Paykel Healthcare France.

**Data collection**

*Data collected preoperatively*: demographic and physical characteristics (age, sex, weight, height, body mass index as weight in kg over height in meters squared), smoking history in pack-years with the dates of smoking initiation and cessation and the mean pack-years of consumption, respiratory function (FEV₁, FEV₁/FVC, FEF 25-75%, FVC and SVC, TLC, PaO₂, and PaCO₂), comorbidities (cardiovascular disease, diabetes, renal dysfunction, and immunosuppression), McCabe score, SOFA score, and SAPS II

*Data collected intraoperatively*: type of surgery, prophylactic antibiotics, prophylactic anticoagulants, and intraoperative complications

*Data collected postoperatively*: heart rate, breathing rate, arterial blood pressure, use of vasoactive agents, arterial blood gas levels (ABG), chest X-ray (at baseline then once a day until discontinuation of the study treatments), duration of the study treatment, and concomitant treatments.

*Complications*: We will record the following complications, whose definitions are provided in the appendix: postoperative pneumonia, atelectasis, surgical-site infection (chest-wall
abscess, empyema, pyothorax, or other), urinary tract infection, catheter-associated bloodstream infection, acute colonic pseudoobstruction, pneumothorax, and prolonged air leaks

Length of stay and mortality in the ICU or intermediate-care unit, length of stay and mortality in the hospital

1) First evaluation, performed at H1:
   - ABG and lactate
   - Breathing rate
   - Systolic and diastolic pressures
   - Heart rate
   - Dyspnea score
   - Comfort score
   - SOFA score

2) Second evaluation, performed between H6 and H12:
   - ABG and lactate
   - Breathing rate
   - Systolic and diastolic pressures
   - Heart rate
   - Dyspnea score
   - Comfort score
   - SOFA score

3) Third evaluation, at H24:
   - ABG and lactate
   - Breathing rate
   - Systolic and diastolic pressures
   - Heart rate
   - Dyspnea score
   - Comfort score
   - SOFA score
   - Skin breakdown score
   - Eye irritation score

4) The worst value of each of the following parameters recorded during the day will be recorded once a day

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Data entry and statistical analysis

The data will be validated by the main investigator then entered into a database by a clinical research organization using the double-entry technique. The database will be registered with the French data protection authority (*Commission Nationale de l'Informatique et des Libertés*, CNIL). After the collection of missing data and resolution of inconsistencies, double data entry will be performed using an electronic data capture application developed specifically for the study. The two files thus obtained will be reconciled and final data cleansing performed. The validated database will then be analyzed using STATVIEW software, under the supervision of Dr Hélène AGOSTINI (URC Centre Chirurgical Marie Lannelongue).

First, we will compute the proportion of eligible patients who were included in the study. We will then describe the two treatment groups based on the data collected for the study. Nominal and ordinal variables will be described as the number and percentage of each modality with the 95% confidence interval. Quantitative variables will be described as the mean and standard deviation if normally distributed and as the median and range otherwise.

Conventional statistical methods will be applied to compare the frequency or value of each outcome measure between the two treatment groups. The chi² test or Fisher’s exact test will be used for comparisons of qualitative variables. Quantitative variables will be compared using Student’s *t* test if normally distributed and the nonparametric Mann-Whitney test otherwise. All analyses will be performed on an intention-to-treat basis. *P* values smaller than 0.05 will be considered significant.

Factors associated with failure or poor tolerance of the study treatments (BiPAP or OPTIFLOW™) will be identified using univariate and multivariate logistic regression.
APPENDIX

1) Dyspnea score (Delclaux et al. JAMA 2000) (32)
+2: marked improvement
+1: slight improvement
0: no change
-1: slight deterioration
-2: marked deterioration

2) Skin breakdown, comfort, and eye irritation scores (Gregoretti et al. Intensive Care Med 2002) (33)

Skin breakdown
0: nil
1: area of redness
2: moderate skin breakdown
3: skin ulcer
4: skin necrosis

Comfort
1: very poor
2: poor
3: sufficient
4: good
5: very good

Eye irritation
0: absent
1: present

3) Operational definitions of postoperative complications
Postoperative pneumonia: Persistent or new infiltrate on the chest X-ray combined with at least two of the following criteria: temperature >38.3 °C or <35 °C, peripheral leukocyte count <4000/mm³ or >12 000/mm³, and purulent tracheal aspirate. Bacteriological confirmation was defined as a positive bacteriological culture from a deep lung specimen (cutoffs: sputum, >10⁷ cfu/mL; tracheal aspirate, 10⁵ cfu/mL; and bronchoalveolar lavage fluid, >10⁴ cfu/mL), pleural fluid, or blood.

Atelectasis: systematized retractile opacity on the chest X-ray

Pulmonary edema: bilateral alveolar opacities (butterfly opacities) on the chest X-ray

Deep incisional surgical-site infections

-Chest-wall abscess: infection within 30 days after surgery, involving the tissues or spaces at or below the level of the superficial fascia, diagnosed based on purulent or cloudy drainage through a drain placed below the fascia or on the presence of any of the following: spontaneous dehiscence of the incision, scar, or chest wall; local pain; tenderness to palpation (except if cultures of wound specimens are negative), or abscess or other evidence of infection during reoperation or upon histological examination of a tissue specimen.

-Pyothorax: infection within 30 days after surgery, involving the pleural space, diagnosed based on drainage of pus or cloudy fluid from a pleural drain, on a positive culture of a pleural fluid specimen, or on clear evidence of pleural space infection during reoperation or upon histological examination of a pleural tissue specimen.

Other nosocomial infections

-Symptomatic urinary tract infection: evidence of infection and/or urinary symptoms and positive urine culture (>10⁵ cfu/mL)
- **Catheter-related bloodstream infection**: catheter-tip culture $>10^3$ cfu/mL with at least one positive blood culture (or at least two positive blood cultures if the organism is *Staphylococcus epidermidis*) or evidence of inflammation at the catheter entry site

- **Acute colonic pseudoobstruction**: obstipation with absence of bowel sounds upon auscultation and abdominal distension

- **Persistent air leakage**: air leakage $>5$ days

4) Sample size calculation

**4.1- Detailed results**

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4.2- References


4.2- Report Definitions

“Power” is the probability of erroneously rejecting the null hypothesis. It should be close to 1.
“N1 and N2” are the numbers of patients in each group.
“P2” is the response rate for the control group.
“P1.0” is the smallest treatment-group response rate consistent with non-inferiority of the study intervention.
“P1.1” is the treatment-group response rate used to compute power.
“Target Alpha” is the probability of rejecting a true null hypothesis that was desired.
“Actual Alpha” is the value of alpha that is actually achieved.
“Beta” is the probability of accepting a false null hypothesis. Beta = 1 - Power.
“Grp 1” (Group 1) is the treatment or experimental group.
“Grp 2” (Group 2) is the control group.
“Equiv.” refers to a small amount that is not of practical importance.
“Actual” refers to the true value used to compute power.