

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

High-Flow Nasal Oxygen vs Noninvasive Positive Airway Pressure in Hypoxemic Patients After Cardiothoracic Surgery

A Randomized Clinical Trial

François Stéphan, MD, PhD; Benoit Barrucand, MD; Pascal Petit, MD; Saida Rézaiguia-Delclaux, MD; Anne Médard, MD; Bertrand Delannoy, MD; Bernard Cosserant, MD; Guillaume Flicoteaux, MD; Audrey Imbert, MD; Catherine Pilorge, MD; Laurence Bérard, MD; for the BiPOP Study Group

IMPORTANCE Noninvasive ventilation delivered as bilevel positive airway pressure (BiPAP) is often used to avoid reintubation and improve outcomes of patients with hypoxemia after cardiothoracic surgery. High-flow nasal oxygen therapy is increasingly used to improve oxygenation because of its ease of implementation, tolerance, and clinical effectiveness.

OBJECTIVE To determine whether high-flow nasal oxygen therapy was not inferior to BiPAP for preventing or resolving acute respiratory failure after cardiothoracic surgery.

DESIGN AND SETTING Multicenter, randomized, noninferiority trial (BiPOP Study) conducted between June 15, 2011, and January 15, 2014, at 6 French intensive care units.

PARTICIPANTS A total of 830 patients who had undergone cardiothoracic surgery, of which coronary artery bypass, valvular repair, and pulmonary thromboendarterectomy were the most common, were included when they developed acute respiratory failure (failure of a spontaneous breathing trial or successful breathing trial but failed extubation) or were deemed at risk for respiratory failure after extubation due to preexisting risk factors.

INTERVENTIONS Patients were randomly assigned to receive high-flow nasal oxygen therapy delivered continuously through a nasal cannula (flow, 50 L/min; fraction of inspired oxygen [FiO_2], 50%) (n = 414) or BiPAP delivered with a full-face mask for at least 4 hours per day (pressure support level, 8 cm H_2O ; positive end-expiratory pressure, 4 cm H_2O ; FiO_2 , 50%) (n = 416).

MAIN OUTCOMES AND MEASURES The primary outcome was treatment failure, defined as reintubation, switch to the other study treatment, or premature treatment discontinuation (patient request or adverse effects, including gastric distention). Noninferiority of high-flow nasal oxygen therapy would be demonstrated if the lower boundary of the 95% CI were less than 9%. Secondary outcomes included mortality during intensive care unit stay, changes in respiratory variables, and respiratory complications.

RESULTS High-flow nasal oxygen therapy was not inferior to BiPAP: the treatment failed in 87 of 414 patients with high-flow nasal oxygen therapy (21.0%) and 91 of 416 patients with BiPAP (21.9%) (absolute difference, 0.9%; 95% CI, -4.9% to 6.6%; $P = .003$). No significant differences were found for intensive care unit mortality (23 patients with BiPAP [5.5%] and 28 with high-flow nasal oxygen therapy [6.8%]; $P = .66$) (absolute difference, 1.2% [95% CI, -2.3% to 4.8%]). Skin breakdown was significantly more common with BiPAP after 24 hours (10% vs 3%; 95% CI, 7.3%-13.4% vs 1.8%-5.6%; $P < .001$).

CONCLUSIONS AND RELEVANCE Among cardiothoracic surgery patients with or at risk for respiratory failure, the use of high-flow nasal oxygen therapy compared with intermittent BiPAP did not result in a worse rate of treatment failure. The findings support the use of high-flow nasal oxygen therapy in similar patients.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The BiPOP Study Group members are listed at the end of this article.

Corresponding Author: François Stéphan, MD, PhD, Réanimation Adulte, Centre Chirurgical Marie Lannelongue, 133 avenue de la Résistance, 92350 Le Plessis Robinson, France (f.stephan@ccml.fr).

Section Editor: Derek C. Angus, MD, MPH, Associate Editor, JAMA (angusdc@upmc.edu).

After cardiothoracic surgery, acute respiratory failure is common and associated with increased morbidity and mortality.^{1,2} When low-flow oxygen therapy is insufficient to correct hypoxemia, noninvasive ventilation is often used to avoid reintubation and improve outcomes,³⁻⁷ notably as a preventive or curative intervention after cardiothoracic surgery.^{4,5} A moderate level of evidence (grade 2) supports noninvasive ventilation to treat postoperative respiratory failure.⁸ However, this technique is difficult to implement, requires substantial resources, and may cause patient discomfort.⁷⁻¹⁰ It fails in approximately 20% of patients after cardiothoracic surgery, who then require reintubation.^{2,7,11,12} High-flow nasal oxygen therapy involves the continuous delivery of up to 60 L/min through a nasal cannula, with optimal heat and humidity. It is increasingly used because of ease of application, patient tolerance, and theoretical clinical benefits¹³⁻¹⁵ and may constitute an important alternative to noninvasive ventilation.

We hypothesized that high-flow nasal oxygen therapy was not inferior to noninvasive ventilation for preventing or resolving acute respiratory failure after cardiothoracic surgery. To assess this hypothesis, we performed a multicenter, randomized, noninferiority trial of high-flow nasal oxygen therapy vs noninvasive ventilation after extubation. The primary outcome was the frequency of treatment failure, and secondary outcomes included early changes in respiratory variables, comfort, and respiratory and extrapulmonary complications.

Methods

Trial Design and Oversight

From June 15, 2011, to January 15, 2014, we recruited patients in 6 intensive care units throughout France (study protocol is in Supplement 1). The trial was approved for all centers by the Comité de Protection des Personnes Ile-de-France VII. Because both study treatments were components of standard care, informed consent was not required by the Comité de Protection des Personnes Ile-de-France. Written and oral information was provided to the patient or relatives. The study was conducted according to the Declaration of Helsinki.

Patients

Patients were eligible if they had undergone cardiothoracic surgery and met any of the following criteria:

1. Failure of a spontaneous breathing trial, defined as arterial oxygen saturation (SaO_2) less than 90% with 12 L of oxygen during a T-tube trial or PaO_2 less than 75 mm Hg with a fraction of inspired oxygen (FiO_2) of at least 50% during low-level pressure support
2. Successful spontaneous breathing trial in patients with any of the following preexisting risk factors for postextubation acute respiratory failure: body mass index greater than 30, left ventricular ejection fraction less than 40%, and failure of previous extubation

3. Successful spontaneous breathing trial followed by failed extubation, defined as at least 1 of the following: $PaO_2:FiO_2$ ratio less than 300, respiratory rate greater than 25/min for at least 2 hours, and use of accessory respiratory muscles or paradoxical respiration.

Exclusion criteria were obstructive sleep apnea, tracheostomy, do-not-intubate status, delirium, nausea and vomiting, bradypnea, impaired consciousness, and hemodynamic instability.

Randomization

Randomization was conducted in blocks of 2 or 4, regardless of entry criteria, with opaque envelopes, with a single computer-generated (nQuery Advisor) random-number sequence for all centers. Attending physicians randomly assigned patients in a 1:1 ratio to one of the 2 groups (Figure 1).

Study Intervention

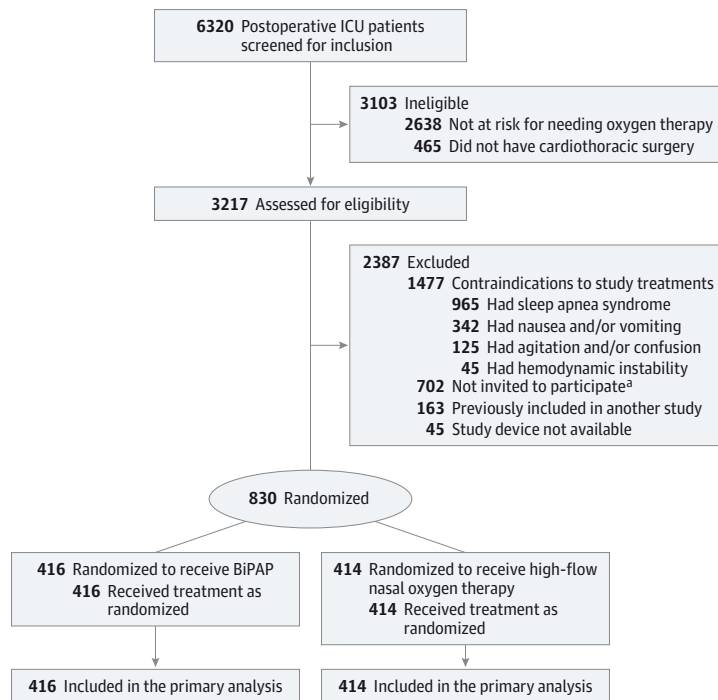
High-flow humidified oxygen (37°C and 44 mg H_2O/L) was delivered continuously through a nasal cannula with Optiflow (Fisher and Paykel Healthcare). The initial flow rate was 50 L/min and the initial FiO_2 was 50%, with subsequent adjustments at the physician's discretion to maintain SaO_2 at 92% to 98%.

Bilevel positive airway pressure (BiPAP) was delivered with a full-face mask and either a ventilator specifically designed for BiPAP (BiPap Vision; Respironics) or an intensive care unit ventilator in pressure-support mode with added positive end-expiratory pressure (Dräger Evita XL or 4, Dräger Medical SAS; or Monnal T75, Air Liquide). Exchange filters for heat and moisture were used. Pressure support was increased, starting at 8 cm H_2O , to achieve an exhaled tidal volume of 8 mL/kg and a respiratory rate less than 25/min. Positive end-expiratory pressure was initially set at 4 cm H_2O . Fraction of inspired oxygen was 50% initially and then was adjusted to maintain SaO_2 at 92% to 98%. Bilevel positive airway pressure was used initially for 2 hours and then for approximately 1 hour every 4 hours, or more if needed to achieve clinical respiratory stability. Between BiPAP sessions, patients received oxygen via a standard nasal cannula, simple face mask, or nonbreathing mask to maintain SaO_2 at 92% or higher. Fraction of inspired oxygen was calculated by assuming that it increased by 3% per liter of oxygen¹⁶; for the nonbreathing mask with a reservoir, FiO_2 was assumed to be 80%.

During the bedside morning round, when FiO_2 was no higher than 50% with high-flow nasal oxygen therapy, oxygen was administered via a nasal probe instead. High-flow nasal oxygen therapy was discontinued if SaO_2 was at least 95% at 6 L/min or the $PaO_2:FiO_2$ ratio was at least 300. Bilevel positive airway pressure was discontinued when fewer than 4 hours per day were needed. The same oxygen therapy method could be resumed within 24 hours after discontinuation if required by the patient's clinical condition. After discontinuation, success was defined as absence of ventilatory support for the next 72 hours.^{3,6}

All patients had an active program of physiotherapy during the postoperative period. Two respiratory therapists routinely visited each patient twice between 7 AM and 7 PM, or more often if needed.

Figure 1. Patient Flowchart of Study of High-Flow Nasal Oxygen Therapy vs Bilevel Positive Airway Pressure in Postoperative Hypoxemia



^a For 702 patients one of the following prevented inclusion into the study: the physician forgot to enroll the patient, the physician did not approve of the study, or the physician did not include patients at night or on weekends.

Follow-up

Arterial blood gas values and respiratory rate were collected at baseline (before any study intervention), after 1 hour, and between 6 and 12 hours; thereafter, the worst value for each respiratory variable was recorded once a day during the following days. Physiologic variables were recorded after 1 hour of BiPAP or high-flow nasal oxygen therapy and then 6 to 12 hours after study-treatment initiation, during BiPAP or standard oxygen therapy (because BiPAP was used intermittently), or during high-flow nasal oxygen therapy (which was used continuously) (eFigure 4 in Supplement 2).

Patients were asked to grade treatment effects on their dyspnea¹⁷ (2, marked improvement; 1, slight improvement; 0, no change; -1 slight deterioration; and -2, marked deterioration) and comfort¹⁸ (1, very poor; 2, poor; 3, sufficient; 4, good; and 5, very good). The degree of skin breakdown was assessed by the nurse or physician¹⁸ (0, none; 1, local erythema; 2, moderate skin breakdown; 3, skin ulcer; and 4, skin necrosis). These 3 scales were assessed once daily in the afternoon.

Study Outcomes

The primary outcome was treatment failure, defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study-treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention). We used predefined criteria for reintubation previously reported by our team,¹⁹ ie, respiratory arrest, respiratory pauses with loss of consciousness or gasping respiration, encephalopathy, cardiovascular instability, unmanageable secre-

tions, clinical signs of exhaustion, refractory hypoxemia (arterial oxygen saturation < 88% with FiO₂ = 100%), or respiratory acidosis (pH < 7.30 and PaCO₂ ≥ 50 mm Hg). Reintubation decisions were made by the attending physicians. An alternative to reintubation was switching to the treatment used in the other study group, although physicians were encouraged to avoid this measure unless the patient had persistent dyspnea, hypoxemia, or hypercapnia greater than 50 mm Hg.

Secondary outcomes included changes in respiratory variables after 1 hour and between 6 and 12 hours, changes in the worst daily values of respiratory variables under treatment, dyspnea score, comfort score, skin breakdown score, respiratory and extrapulmonary complications, and number of bronchoscopies. Fiberoptic bronchoscopy was performed at the discretion of the attending physician and was available 24 hours a day. Post hoc exploratory outcomes included number of nurse interventions for unplanned device displacement and mortality. The period within which all occurred was the intensive care unit stay. Nurse interventions for unplanned device displacement were recorded during the entire time when treatment was provided. The attending nurse did not count the time needed to put the device in place as scheduled.

Definitions of Respiratory and Extrapulmonary Complications

We recorded cases of pneumothorax and acute colonic pseudo-obstruction (cecal diameter ≥ 10 cm on radiographs or neostigmine administration) during spontaneous ventilation. Nosocomial pneumonia was defined by a clinical suspicion with positive bacteriologic culture results from deep lung specimens and was recorded throughout the intensive care unit stay.

Statistical Analysis

In accordance with previous studies,^{12,19} we estimated that BiPAP would fail in 20% of patients. In a previous study,²⁰ the absolute difference in the frequency of treatment failure between BiPAP and low-flow oxygen therapy was 16% (95% CI, 1.9%-29.4%).

We set the noninferiority margin at 9% according to data reported by Ferrer et al²⁰ and after discussion with contributing physicians representing the BiPOP study group, who stated that this noninferiority margin at 9% would be clinically relevant. To assess noninferiority of high-flow nasal oxygen with $\alpha = .05$, $\beta = .20$, and 1-sided testing, 840 participants were needed. Noninferiority of high-flow nasal oxygen therapy would be demonstrated if the lower boundary of the 95% CI were less than 9%. The noninferiority hypothesis applied only to the primary end point. For all secondary outcomes, we hypothesized that high-flow nasal oxygen therapy was superior to BiPAP. A 2-sided α value was used for superiority testing.

All analyses were performed on an intention-to-treat basis. Baseline categorical characteristics were described as number (%) and quantitative variables as means (95% CI) or median (interquartile range).

For the analysis of secondary outcomes, dichotomous variables were compared with the χ^2 test or Fisher test, as appropriate. We used 3 categories for the dyspnea scale results (improvement, 2 or 1; no improvement, 0; and deterioration, -1 or -2) and comfort scale results (poor, 1 or 2; acceptable, 3; and good, 4 or 5) and then analyzed these categories as dichotomous repeated variables, using the McNemar test. Continuous variables were compared with the *t* test or Wilcoxon rank sum test. For quantitative repeated variables (physiologic variables at baseline, after 1 hour, and after 6 to 12 hours), a linear mixed-effects model was built to compare the 2 study interventions, with subject as a random effect and graphic verification of model validity. For multiple between-group comparisons at baseline, after 1 hour, and after 6 to 12 hours, we applied the Bonferroni correction. Statistical significance was defined as $P \leq .05$.

A descriptive analysis of data with repeated measures was conducted for all patients during the first 3 days. Because the treatment failed or was successful in some patients within that period, the number of patients analyzed decreased between days 1 and 3; we therefore performed exploratory analyses of repeated measurements of clinically relevant quantitative data during the first 3 days, using a linear mixed-effects model to compare the 2 study interventions, with subject as a random effect and graphic verification of model validity. For multiple between-group comparisons, we applied the Bonferroni correction.

All analyses were performed with R software version 3.1.0 (<http://www.r-project.org>). Linear mixed-effects models were built with the RVAideMemoire package.

Results

Study Patients

We randomized 830 patients (Figure 1), all of whom completed the study. Acute respiratory failure was the inclusion criterion in 240 patients (57.7%) allocated to BiPAP and 248

(59.9%) allocated to high-flow nasal oxygen therapy. Baseline characteristics were similar in the 2 groups (Table 1). Patients with an average age of 64 years in each group had undergone cardiothoracic surgery, of which coronary artery bypass, valvular repair, and pulmonary thromboendarterectomy were the most common. Approximately 80% of patients in each group were operated on with cardiopulmonary bypass.

Primary Outcome

High-flow nasal oxygen therapy was not inferior to BiPAP: with BiPAP, treatment failure occurred in 91 of 416 patients (21.9%; 95% CI, 18.0%-26.2%) compared with 87 of 414 (21.0%; 95% CI, 17.2%-25.3%) with high-flow nasal oxygen. The risk difference was 0.9% (95% CI, -4.9% to 6.6%; $P = .003$). Median time from treatment initiation to treatment failure was 1.0 day with BiPAP (interquartile range, 0-2.0 days) vs 1.0 day with high-flow nasal oxygen therapy (interquartile range, 0-2.0 days) ($P = .96$) (Figure 2). Reintubation was performed in 57 patients with BiPAP (13.7%) and 58 with high-flow nasal oxygen therapy (14.0%) ($P = .99$). Switching to the other study treatment occurred for 33 patients with BiPAP (7.9%; 95% CI, 5.6%-11.0%) and 45 with high-flow nasal oxygen therapy (10.8%; 95% CI, 8.5%-14.9%) ($P = .15$). Premature discontinuation was noted for 15 patients with BiPAP (3.6%; 95% CI, 2.1%-6.0%) and 6 with high-flow nasal oxygen therapy (1.4%; 95% CI, 0.6%-3.3%) ($P = .04$). Details on treatment failures are provided in eFigure 1 in Supplement 2. Reasons for reintubation are reported in eTable 1 in Supplement 2. Patients who underwent reoperation were systematically intubated and considered a failure.

In a sensitivity analysis exploring the effect in patients with more severe hypoxia ($\text{PaO}_2:\text{FiO}_2$ ratio <200), BiPAP failed in 58 of 234 patients (24.8%; 95% CI, 19.5%-30.9%) and high-flow nasal oxygen therapy in 66 of 240 (27.5%; 95% CI, 22.0%-33.7%) ($P = .50$).

Respiratory Variables

Courses of respiratory variables are reported in Table 2. Six to 12 hours after BiPAP initiation, mean tidal volume was 7.2 mL/kg (SD, 3.4 mL/kg), mean inspiratory pressure 9.3 cm H₂O (SD, 2.6 cm H₂O), and mean expiratory pressure 4.2 cm H₂O (SD, 1.0 cm H₂O). In the high-flow nasal oxygen therapy group, mean preset flow was 46.7 L/min (SD, 4.9 L/min).

Respiratory support was required throughout the first 3 days for 304 patients: 153 in the BiPOP group and 151 in the high-flow nasal oxygen group. $\text{PaO}_2:\text{FiO}_2$ increased from day 1 to day 3 in both groups: from 160 (95% CI, 149-170) to 187 (95% CI, 173-202) in the BiPAP group and from 136 (95% CI, 127-145) to 157 (95% CI, 145-169) in the high-flow nasal oxygen group ($P < .001$) but was significantly higher with BiPAP ($P < .001$) (eFigure 2 in Supplement 2). Respiratory rate was significantly higher with BiPAP from day 1 to day 3: from 29.7/min (95% CI, 28.6-30.7) to 28.4/min (95% CI, 27.5-29.4) in BiPAP group and 26.7/min (95% CI, 25.7-27.7) in high-flow nasal oxygen group ($P < .001$) and remained significantly higher with BiPAP. Paco_2 was similar between groups from day 1 to day 3: from 39.5 mm Hg (95% CI, 38.3-40.6) to 39.1 mm Hg (95% CI, 38.0-40.2) in BiPAP group and from 38.8 mm Hg (95% CI, 37.8-39.8) to 38.3 mm Hg (95% CI, 37.1-39.4) in the high-flow nasal oxygen group; ($P = .20$) (eFigure 2 and eFigure 3 in Supplement 2).

Table 1. Patient Characteristics

Characteristics	BiPAP (n = 416)	High-Flow Nasal Oxygen Therapy (n = 414)
Age, mean (95% CI), y	63.9 (62.6-65.2)	63.8 (62.5-65.2)
Men, No. (%)	278 (66.8)	273 (65.9)
Body mass index ^a		
Mean (95% CI)	28.2 (27.6-28.7)	28.3 (27.8-28.8)
>30, No. (%)	136 (32.7)	135 (32.6)
Smoking, No. (%) ^b		
Former	217 (52.2)	226 (54.6)
Current	69 (16.6)	83 (20.0)
SAPS II score at admission, mean (95% CI)	28.8 (27.7-30.0)	29.0 (27.8-30.1)
Surgical procedures, No. (%)		
Coronary artery bypass grafting	111 (26.7)	122 (29.5)
Valvular surgery	83 (20.0)	88 (21.3)
Combined cardiac surgery with coronary artery bypass grafting	27 (6.5)	26 (6.3)
Thoracic aorta	28 (6.7)	23 (5.6)
Pulmonary thromboendarterectomy	90 (21.6)	68 (16.4)
Lung resection	30 (7.2)	34 (8.2)
Heart, lung, and heart-lung transplantations	9 (2.2)	18 (4.3)
Others	38 (9.1)	35 (8.5)
Cardiopulmonary bypass, No. (%)	340 (81.7)	320 (77.2)
Duration of cardiopulmonary bypass, mean (95% CI), min	137 (129-146)	137 (128-146)
Time from surgery to randomization, median (IQR), d	1.0 (1.0-3.0)	1.0 (1.0-3.0)
Duration of mechanical ventilation at randomization, median (IQR), h	13.0 (6.0-27.5)	11.5 (5.0-25.4)

Abbreviations: BiPAP, bilevel positive airway pressure; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score Version II.

^a Body mass index is calculated as weight in kilograms divided by height in meters squared.

^b Spirometry results were available for 559 patients: 288 (69.2%) in the BiPAP group and 271 (65.4%) in the high-flow nasal oxygen group. According to the spirometry classification, chronic obstructive pulmonary disease was mild to moderate in 68 patients (23%) in the BiPAP group and 47 (17%) in the high-flow nasal oxygen group; it was severe in 5 patients (2%) in each group.

Clinical Outcomes and Adverse Events

Dyspnea and comfort scores during the first 3 days were similar in both groups. The proportion of patients with skin breakdown during the first 2 days was higher in the BiPAP group (Table 3).

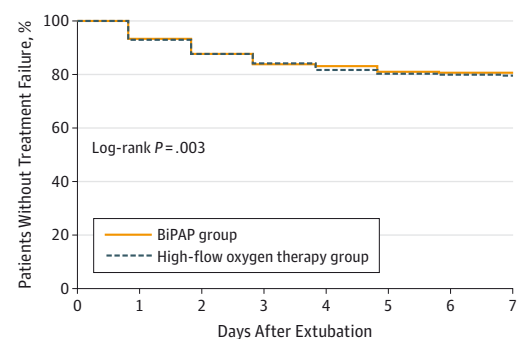
No significant differences were found for intensive care unit mortality (23 patients with BiPAP [5.5%; 95% CI, 3.6%-8.3%] and 28 patients with high-flow nasal oxygen therapy [6.8%; 95% CI, 4.6%-9.7%]; *P* = .66) or for any of the other secondary outcomes, including number of nurse interventions for unplanned device readjustment (Table 3 and Table 4). Causes of death in the intensive care unit are reported in eTable 2 in Supplement 2.

Discussion

This multicenter, randomized, unblinded trial with 830 patients showed that high-flow nasal oxygen therapy was not inferior to BiPAP for patients with hypoxemia after cardiothoracic surgery. Effects on respiratory variables were rapid with both methods. BiPAP was associated with a higher PaO₂:FIO₂ ratio; high-flow nasal oxygen therapy, with lower values for PaCO₂ and respiratory rate. High-flow nasal oxygen therapy had no effect on frequencies of adverse events or stay lengths in the intensive care unit or hospital.

Severe hypoxemia is common after cardiothoracic surgery^{1,2} and is often treated or prevented with noninvasive ventilation,^{4,5,7-9} a method reported to improve outcomes of hypoxemic patients after thoracic^{11,19,23,24} or cardiac^{12,25-27} sur-

Figure 2. Postoperative Patients Without Treatment Failure After Extubation



No. at risk	416	385	363	348	339	333	331	329
BiPAP								
High-flow oxygen therapy	414	385	361	346	342	334	333	331

Percentages of patients in whom treatment with either bilevel positive airway pressure (BiPAP) or high-flow nasal oxygen did not fail after postoperative extubation. Treatment failure occurred in 91 of 416 patients with BiPAP (21.9%) and 87 of 414 patients with high-flow nasal oxygen therapy (21.0%) (absolute difference, 0.86%). Treatment failure was defined as reintubation for mechanical ventilation, switch to the other study treatment, or premature study treatment discontinuation (at the request of the patient or for medical reasons such as gastric distention).

gery, decreasing the risk of pulmonary complications and reintubation.^{8,9} However, high-flow nasal oxygen therapy is increasingly used for critically ill adults.¹³ In nonsurgical hypoxemic patients, compared with low-flow oxygen therapy,

Table 2. Physiologic Variables and Subjective Effect on Dyspnea at Baseline (Before Any Study Intervention), After 1 Hour, and After 6-12 Hours

Parameters	Mean (95% CI)							
	Baseline		1 Hour		P Value	6-12 Hours		P Value
	BiPAP Group	HFNO Group	BiPAP Group	HFNO Group		BiPAP Group	HFNO Group	
PaO ₂ :Fio ₂	203 (195-212)	196 (187-204)	221 (213-230) ^a	184 (177-192) ^b	<.001	261 (248-274) ^c	198 (187-208) ^c	<.001
Paco ₂ , mm Hg	39.1 (38.4-39.8)	38.7 (38.1-39.4)	39.0 (38.4-39.7)	37.9 (37.2-38.5) ^d	.09	39.3 (38.6-40.0)	38.2 (37.6-38.9)	.19
pH	7.39 (7.39-7.40)	7.39 (7.39-7.40)	7.39 (7.39-7.40)	7.40 (7.39-7.40)	.75	7.40 (7.40-7.41) ^e	7.41 (7.40-7.42) ^f	.99
Respiratory rate, breaths/min	23.3 (22.6-24.0)	22.8 (22.1-23.5)	23.0 (22.3-23.7)	21.0 (20.4-21.7) ^a	<.001	22.5 (21.9-23.1)	21.6 (20.9-22.2)	.16
Actual or calculated Fio ₂	0.47 (0.45-0.49)	0.49 (0.47-0.51)	0.55 (0.53-0.57)	0.60 (0.59-0.62)	<.001	0.53 (0.51-0.56)	0.58 (0.57-0.60)	<.001
Dyspnea score, No./total (%) [95% CI]								
Improvement			266/404 (65.8) [61.0-70.7]	236/403 (58.6) [53.6-63.4]		229/379 (60.4) [55.3-65.4]	217/373 (58.2) [52.9-63.2]	
No improvement			120/404 (29.7) [25.3-34.4]	151/403 (37.5) [32.7-42.4]	.39	133/379 (35.1) [30.3-40.1]	139/373 (37.3) [32.4-43.4]	.99
Deterioration			18/404 (4.5) [2.7-7.0]	16/403 (4.0) [2.3-6.4]		17/379 (4.5) [2.6-6.1]	17/373 (4.6) [2.7-7.2]	
Comfort score, No. (%) [95% CI]								
Poor			51/397 (13.0) [9.7-16.5]	67/402 (16.7) [13.2-20.7]		67/376 (17.8) [14.1-22.1]	66/372 (17.7) [14.0-22.0]	
Acceptable			128/397 (32.2) [27.7-37.1]	101/402 (25.1) [21.0-29.7]	.32	110/376 (29.3) [24.7-34.1]	115/372 (31.0) [26.3-36.9]	.99
Good			218/397 (55.0) [49.9]	234/402 (58.2) [53.2-63.1]		199/376 (53.0) [47.7-58.1]	101/372 (51.0) [46.1-56.5]	

Abbreviations: BiPAP, bilevel positive airway pressure; Fio₂, fraction of inspired oxygen; HFNO, high-flow nasal oxygen therapy.

^a Within-group comparison with Bonferroni correction, 1 hour vs baseline: P < .001.

^b Within-group comparison with Bonferroni correction, 1 hour vs baseline: P = .004.

^c Within-group comparison with Bonferroni correction, 6-12 hours vs 1 hour: P < .001.

^d Within-group comparison with Bonferroni correction, 1 hour vs baseline: P = .02.

^e Within-group comparison with Bonferroni correction, 6-12 hours vs 1 hour: P = .002.

^f Within-group comparison with Bonferroni correction, 1 hour vs baseline: P = .001.

high-flow nasal oxygen therapy was associated with better comfort, fewer desaturation episodes and interface displacements, and a lower reintubation rate.¹³ However, few studies suggest that high-flow nasal oxygen therapy may be more effective than low-flow oxygen therapy in improving oxygenation^{14,15,28} and comfort¹⁴ after cardiothoracic surgery.

It has been reported that noninvasive ventilation used preventively did not affect the frequency of reintubation,²⁹ which was only 5.5% after thoracic surgery³⁰ and less than 2% after cardiac surgery.²⁶ Thus, there may be room for improvement in selecting patients likely to benefit from noninvasive ventilation.^{6,31} In our study, BiPAP or high-flow nasal oxygen therapy was used prophylactically only for patients with risk factors for respiratory failure after extubation: obesity,³² heart failure,^{6,20,33} and failure of spontaneous breathing trial.³

With noninvasive ventilation used to treat respiratory failure, the need for subsequent intubation ranges from 19% to 30%.^{11,12,19,23,27} A single randomized trial found that noninvasive ventilation after lung resection decreased the frequency of intubation from 50.0% to 20.8% and also decreased

mortality.¹¹ Both reintubation and mortality rates decreased significantly with noninvasive ventilation in the single published randomized study after heart surgery; the frequency of reintubation decreased from 80.9% to 18.8%.¹² We defined failure of each study treatment as reintubation or switch to the other study treatment or premature discontinuation of the randomly allocated treatment. Despite the subjective component of the 2 last criteria, this definition helped us to replicate everyday clinical practice. The reasons for reintubation were not different between the 2 groups. In a general population of patients with respiratory failure after extubation, mortality was higher with noninvasive ventilation.³⁴ We found low and similar mortality rates in the 2 groups. The considerable skill and experience required to administer noninvasive ventilation may contribute to discrepancies across studies.¹⁰

Oxygenation improved more with BiPAP, as previously reported,³⁵ perhaps because of the higher positive end-expiratory pressure compared with high-flow nasal oxygen therapy.^{36,37} Unexpectedly, Paco₂ decreased faster during high-flow nasal oxygen therapy, with possible explanations being a higher tidal

Table 3. Subjective Effect on Dyspnea, Comfort Score, Nurse Interventions, and Markers of Illness Severity During the First 3 Study Treatment Days^a

Parameters	Day 1		Day 2		Day 3		P Value
	BIPAP (n = 412)	High-Flow Nasal Oxygen Therapy (n = 408)	BIPAP (n = 272)	High-Flow Nasal Oxygen Therapy (n = 257)	BIPAP (n = 153)	High-Flow Nasal Oxygen Therapy (n = 151)	
Duration of respiratory assistance per day, mean (95% CI), h	6.6 (6.3-6.9)	17.9 (17.3-18.6)	6.5 (6.0-6.9)	20.7 (19.9-21.4)	6.0 (5.4-6.6)	20.5 (19.4-21.6)	
Dyspnea score, No./total (%) [95% CI]							
Improvement	227/402 (56.5) [51.5-61.4]	224/396 (56.6) [51.5-61.5]	174/261 (66.7) [60.6-72.3]	163/252 (64.7) [58.4-72.6]	98/142 (69.0) [60.7-76.5]	87/148 (58.8) [50.4-66.8]	
No improvement	146/402 (36.3) [31.6-41.2]	134/396 (33.8) [29.2-38.7]	76/261 (29.1) [23.7-35.0]	76/252 (30.2) [24.6-36.2]	34/142 (23.9) [17.2-31.8]	50/148 (34.0) [26.2-42.0]	.48
Deterioration	29/402 (7.2) [4.9-10.2]	38/396 (9.6) [6.9-12.9]	11/261 (4.2) [2.1-7.4]	13/252 (5.2) [2.8-8.7]	10/142 (7.0) [3.4-12.6]	11/148 (7.4) [3.8-12.9]	
Comfort score, No./total (%) [95% CI]							
Poor	86/399 (21.6) [17.6-25.9]	81/395 (20.5) [16.6-26.9]	56/261 (21.5) [16.6-26.9]	52/249 (21.0) [16.0-26.5]	30/143 (21.0) [14.6-28.6]	31/148 (21.0) [14.7-28.4]	
Acceptable	118/399 (29.6) [25.1-34.3]	116/395 (29.4) [24.9-34.1]	76/261 (29.1) [23.7-35.0]	80/249 (32.1) [26.4-38.3]	44/143 (31.0) [23.3-39.0]	48/148 (32.4) [24.9-40.6]	>.99
Good	195/399 (49.0) [43.9-53.9]	198/395 (50.1) [45.1-55.2]	129/261 (49.4) [43.2-55.7]	117/249 (47.0) [40.7-53.4]	69/143 (48.3) [39.8-56.7]	69/148 (47.0) [38.4-55.0]	
Skin breakdown, No./total (%) [95% CI]							
None	363/403 (90.1) [86.6-92.7]	392/405 (96.8) [94.4-98.2]	229/267 (86.0) [80.9-89.6]	232/252 (92.1) [87.8-94.9]	119/145 (82.1) [74.6-87.8]	129/147 (87.8) [81.0-92.4]	
Focal erythema	38/403 (9.4) [6.8-12.8]	10/405 (2.5) [1.3-4.6]	38/267 (14.2) [10.4-19.1]	19/252 (7.5) [4.7-11.7]	25/145 (17.2) [11.7-24.6]	18/147 (12.2) [7.6-19.8]	>.99
Moderate skin breakdown	1/403 (0.2)	2/405 (0.5)	0	0	1/145 (0.7)	0	
Skin ulcer	0	1/405 (0.2)	0	1/252 (0.4)	0	0	
Skin necrosis	1/403 (0.2)	0	0	0	0	0	
Nurse interventions per patient, mean (95% CI)	0.30 (0.22-0.38)	0.49 (0.34-0.63)	0.24 (0.15-0.32)	0.39 (0.26-0.52)	0.29 (0.14-0.45)	0.32 (0.20-0.43)	.24
Patients with ≥1 fiberoptic bronchoscopy, No. (%) [95% CI]	31 (7.5) [5.4-10.9]	40 (9.8) [7.4-13.6]	28 (10.3) [7.3-15.2]	27 (10.5) [7.4-15.6]	12 (7.8) [4.3-13.8]	22 (14.6) [10.2-22.9]	.20
Score, mean (95% CI)							
Radiologic ^b	4.0 (3.8-4.2)	4.3 (4.1-4.5)	4.2 (3.9-4.4)	4.5 (4.2-4.7)	4.5 (4.2-4.8)	4.7 (4.4-5.0)	>.99
SOFA ^c	4.7 (4.5-4.9)	4.9 (4.6-5.1)	4.4 (4.2-4.7)	4.7 (4.4-4.9)	4.2 (3.9-4.5)	4.8 (4.4-5.2)	.03

Abbreviations: BIPAP, bilevel positive airway pressure; SOFA, Sequential Organ Failure Assessment. anterior-posterior chest roentgenograms were divided into 4 zones, using a horizontal line originating from the hilus. Each zone was then graded as follows: 0, normal; 1, interstitial pulmonary infiltrates; 2, fluffy alveolar infiltrates; and 3, dense alveolar infiltrates. Thus, the score could range from 0 to 12, with higher scores indicating greater severity of infiltration.

^a P values for between-group comparisons at each time point, not adjusted for multiple comparisons. Qualitative variables were compared using a global Fisher test with Bonferroni correction. SOFA scores and nurse interventions per patient were compared using a Wilcoxon rank-sum test. Radiologic scores were compared using a t test.

^b The radiologic score was determined with a modification of the technique described by Weinberg et al.²¹ Briefly, SOFA score range = 0 to 24; higher scores indicate more severe illness.²²

Table 4. Clinical Outcomes and Adverse Events During the Intensive Care Unit Stay

Events	Group		P Value
	BiPAP (n = 416)	HFNO (n = 414)	
Nosocomial pneumonia, No. (%) [95% CI]	90 (21.6) [17.8-25.9]	83 (20.0) [16.4-24.3]	.57
Pneumothorax, No. (%) [95% CI]	7 (1.7) [0.7-3.6]	8 (1.9) [0.9-3.9]	.86
Acute colonic pseudo-obstruction, No. (%) [95% CI]	8 (1.9) [0.9-3.9]	9 (2.2) [1.0-4.2]	.86
No. of days with respiratory support, median (IQR)	2 (1-3)	2 (1-3)	.59
Stay length, median (IQR), d			
ICU	6 (4-10)	6 (4-10)	.77
Hospital	14 (9-20)	13 (9-22)	.59

Abbreviations: BiPAP, bilevel positive airway pressure; HFNO, high-flow nasal oxygen therapy; ICU, intensive care unit; IQR, interquartile range.

volume and improved inspiratory flow dynamics,^{37,38} a carbon dioxide washout effect,¹⁶ and nearly unidirectional breathing.³⁹ Some differences could be explained by the continuity of the treatment. Bilevel positive airway pressure was applied continuously until clinical respiratory stability was obtained and intermittently thereafter, whereas high-flow nasal oxygen was applied continuously with a low level of positive airway pressure during inspiration and expiration.⁴⁰ Effects on dyspnea were similar with the 2 treatments. Good tolerance of high-flow nasal oxygen has been reported.³⁵ However, 20% of our patients experienced persistent marked discomfort with either treatment method. Skin breakdown⁸ was significantly more common in the BiPAP group. It has been reported as nearly consistent after 12 consecutive hours of noninvasive ventilation.¹⁸ Nasal trauma was less common in infants treated with high-flow nasal oxygen therapy compared with noninvasive ventilation.⁴¹

Nursing care action for unplanned device readjustments was similar between the 2 groups and consistent with that of a recent study.³⁸ However, we did not count the time needed to put the device in place, which had to be done 6 times per 24 hours with BiPAP vs only once with high-flow nasal oxygen therapy. A lower nurse workload was noted with high-flow nasal oxygen therapy. The similar frequency of bronchoscopy in the 2 groups probably reflects the use of the same protocols for secretion and atelectasis management⁴² and for confirming suspected pneumonia.

Our results suggest that high-flow nasal oxygen therapy could be used as a first option because it does not hamper the patient's prognosis and it provides some advantages, such as ease of application and lower nursing workload. However, our

results indicate that high-flow oxygen therapy could in fact be worse by up to 4.9%.

Our study has several limitations. First, one of the main considerations in designing it was the proven efficacy of noninvasive ventilation in acute respiratory failure after cardiothoracic surgery. Therefore, we did not consider using the low-flow oxygen device and chest physiotherapy as the comparator. Most physicians now use noninvasive ventilation to treat postoperative acute respiratory failure and are confident of the efficacy of this method.⁵ Moreover, in 2 well-conducted studies, noninvasive ventilation decreased mortality compared with standard treatment^{11,12} This method is therefore widely used.^{4,5} Second, BiPAP or high-flow nasal oxygen therapy was used for preventive or curative treatment. These 2 situations may be difficult to differentiate when noninvasive ventilation is used.³¹ Third, although we applied predefined criteria for reintubation or complications, bias cannot be completely ruled out because blinding was not feasible. Fourth, the FI_{O_2} delivered between BiPAP sessions was calculated instead of measured. Calculated fractions are often higher than measured ones, and we may therefore have underestimated the $Pa_{O_2}:FI_{O_2}$ ratio in the BiPAP group.

Conclusions

Among patients undergoing cardiothoracic surgery with or at risk for respiratory failure, the use of high-flow nasal oxygen compared with intermittent BiPAP did not result in a worse rate of treatment failure. The findings support the use of high-flow nasal oxygen therapy in this patient population.

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Author Affiliations: Service de Réanimation Adulte, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France (Stéphan, Rézaiguia-Delclaux, Imbert, Pilorge); Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire, Besançon, France (Barrucand, Petit, Flicoteaux); Département d'Anesthésie-Réanimation, Centre Hospitalier Universitaire, Clermont Ferrand, France (Médard, Cosserant); Département

d'Anesthésie-Réanimation Centre Hospitalier Universitaire, Lyon, France (Delannoy); Hôpital St Antoine, Plateforme de recherche Clinique de l'Est Parisien, Paris, France (Bérard).

Author Contributions: Dr Stéphan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Stéphan, Rézaiguia-Delclaux, Imbert, Pilorge.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Stéphan, Bérard.

Critical revision of the manuscript for important intellectual content: Barrucand, Petit, Rézaiguia-Delclaux, Médard, Delannoy, Cosserant, Flicoteaux, Imbert, Pilorge.

Statistical analysis: Bérard.

Administrative, technical, or material support: Stéphan, Petit, Médard, Delannoy.

Study supervision: Stéphan, Cosserant.

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REFERENCES

- Xue FS, Li BW, Zhang GS, et al. The influence of surgical sites on early postoperative hypoxemia in adults undergoing elective surgery. *Anesth Analg*. 1999;88(1):213-219.
- Ranucci M, Ballotta A, La Rovere MT, Castelvechio S; Surgical and Clinical Outcome Research (SCORE) Group. Postoperative hypoxia and length of intensive care unit stay after cardiac surgery: the underweight paradox? *PLoS One*. 2014;9(4):e93992.
- Boles J-M, Bion J, Connors A, et al. Weaning from mechanical ventilation. *Eur Respir J*. 2007;29(5):1033-1056.
- Crimi C, Noto A, Princi P, Esquinas A, Nava S. A European survey of noninvasive ventilation practices. *Eur Respir J*. 2010;36(2):362-369.
- Guarracino F, Cabrini L, Ferro B, et al. Noninvasive ventilation practice in cardiac surgery patients: insights from a European survey. *J Cardiothorac Vasc Anesth*. 2013;27(5):e63-e65.
- Thille AW, Richard J-CM, Brochard L. The decision to extubate in the intensive care unit. *Am J Respir Crit Care Med*. 2013;187(12):1294-1302.
- Ozsancak Ugurlu A, Sidhom SS, Khodabandeh A, et al. Use and outcomes of noninvasive positive pressure ventilation in acute care hospitals in Massachusetts. *Chest*. 2014;145(5):964-971.
- Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet*. 2009;374(9685):250-259.
- Jaber S, Chanques G, Jung B. Postoperative noninvasive ventilation. *Anesthesiology*. 2010;112(2):453-461.
- Truweit JD, Bernard GR. Noninvasive ventilation—don't push too hard. *N Engl J Med*. 2004;350(24):2512-2515.
- Auriant I, Jallot A, Hervé P, et al. Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. *Am J Respir Crit Care Med*. 2001;164(7):1231-1235.
- Zhu G-F, Wang DJ, Liu S, Jia M, Jia S-J. Efficacy and safety of noninvasive positive pressure ventilation in the treatment of acute respiratory failure after cardiac surgery. *Chin Med J (Engl)*. 2013;126(23):4463-4469.
- Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. *Intensive Care Med*. 2013;39(2):247-257.
- Nicolet J, Poulard F, Baneton D, Rigal J-C, Blanloeil Y. Oxygénation nasale à haut débit pour hypoxémie après chirurgie cardiaque. *Ann Fr Anesth Reanim*. 2011;30(4):331-334.
- Parke R, McGuinness S, Dixon R, Jull A. Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. *Br J Anaesth*. 2013;111(6):925-931.
- Ward JJ. High-flow oxygen administration by nasal cannula for adult and perinatal patients. *Respir Care*. 2013;58(1):98-122.
- Delclaux C, L'Her E, Alberti C, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. *JAMA*. 2000;284(18):2352-2360.
- Gregoretti C, Confalonieri M, Navalesi P, et al. Evaluation of patient skin breakdown and comfort with a new face mask for non-invasive ventilation: a multi-center study. *Intensive Care Med*. 2002;28(3):278-284.
- Riviere S, Monconduit J, Zarka V, et al. Failure of noninvasive ventilation after lung surgery: a comprehensive analysis of incidence and possible risk factors. *Eur J Cardiothorac Surg*. 2011;39(5):769-776.
- Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med*. 2006;173(2):164-170.
- Weinberg PF, Matthay MA, Webster RO, Roskos KV, Goldstein IM, Murray JF. Biologically active products of complement and acute lung injury in patients with the sepsis syndrome. *Am Rev Respir Dis*. 1984;130(5):791-796.
- Vincent JL, Moreno R, Takala J, et al; on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22(7):707-710.
- Lefebvre A, Lorut C, Alifano M, et al. Noninvasive ventilation for acute respiratory failure after lung resection: an observational study. *Intensive Care Med*. 2009;35(4):663-670.
- Michelet P, D'Journo XB, Seinaye F, Forel JM, Papazian L, Thomas P. Non-invasive ventilation for treatment of postoperative respiratory failure after oesophagectomy. *Br J Surg*. 2009;96(1):54-60.
- Matte P, Jacquet L, Van Dyck M, Goenen M. Effects of conventional physiotherapy, continuous positive airway pressure and non-invasive ventilatory support with bilevel positive airway pressure after coronary artery bypass grafting. *Acta Anaesthesiol Scand*. 2000;44(1):75-81.
- Zarbock A, Mueller E, Netzer S, Gabriel A, Feindt P, Kindgen-Milles D. Prophylactic nasal continuous positive airway pressure following cardiac surgery protects from postoperative pulmonary complications: a prospective, randomized, controlled trial in 500 patients. *Chest*. 2009;135(5):1252-1259.
- Boeken U, Schurr P, Kurt M, Feindt P, Lichtenberg A. Early reintubation after cardiac operations: impact of nasal continuous positive airway pressure (nCPAP) and noninvasive positive pressure ventilation (NPPV). *Thorac Cardiovasc Surg*. 2010;58(7):398-402.
- Corley A, Caruana LR, Barnett AG, Tronstad O, Fraser JF. Oxygen delivery through high-flow nasal cannulae increase end-expiratory lung volume and reduce respiratory rate in post-cardiac surgical patients. *Br J Anaesth*. 2011;107(6):998-1004.
- Lin C, Yu H, Fan H, Li Z. The efficacy of noninvasive ventilation in managing postextubation respiratory failure: a meta-analysis. *Heart Lung*. 2014;43(2):99-104.
- Lorut C, Lefebvre A, Planquette B, et al. Early postoperative prophylactic noninvasive ventilation after major lung resection in COPD patients: a randomized controlled trial. *Intensive Care Med*. 2014;40(2):220-227.
- Jaber S, Antonelli M. Preventive or curative postoperative noninvasive ventilation after thoracic surgery: still a grey zone? *Intensive Care Med*. 2014;40(2):280-283.
- El-Solh AA, Aquilina A, Pineda L, Dhanvantri V, Grant B, Bouquin P. Noninvasive ventilation for prevention of post-extubation respiratory failure in obese patients. *Eur Respir J*. 2006;28(3):588-595.
- Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Crit Care Med*. 2005;33(11):2465-2470.
- Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350(24):2452-2460.
- Schwabbauer N, Berg B, Blumenstock G, Haap M, Hetzel J, Riessen R. Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). *BMC Anesthesiol*. 2014;14:66.
- Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth*. 2009;103(6):886-890.
- Mündel T, Feng S, Tatkov S, Schneider H. Mechanisms of nasal high flow on ventilation during wakefulness and sleep. *J Appl Physiol (1985)*. 2013;114(8):1058-1065.
- Maggiore SM, Idrone FA, Vaschetto R, et al. Nasal high-flow versus Venturi mask oxygen therapy after extubation: effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med*. 2014;190(3):282-288.
- Jiang Y, Liang Y, Kacmarek RM. The principle of upper airway unidirectional flow facilitates breathing in humans. *J Appl Physiol (1985)*. 2008;105(3):854-858.
- Spoletini G, Alotaibi M, Blasi F, Hill NS. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest*. doi:10.1378/chest.14-2871.
- Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med*. 2013;369(15):1425-1433.
- Servera E, Sancho J, Zafrá MJ, Marín J. Secretion management must be considered when reporting success or failure of noninvasive ventilation. *Chest*. 2003;123(5):1773.