Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery
A Randomized Clinical Trial

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IMPORTANCE It has not been established whether noninvasive ventilation (NIV) reduces the need for invasive mechanical ventilation in patients who develop hypoxemic acute respiratory failure after abdominal surgery.

OBJECTIVE To evaluate whether noninvasive ventilation improves outcomes among patients developing hypoxemic acute respiratory failure after abdominal surgery.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, parallel-group clinical trial conducted between May 2013 and September 2014 in 20 French intensive care units among 293 patients who had undergone abdominal surgery and developed hypoxemic respiratory failure (partial oxygen pressure <60 mm Hg or oxygen saturation [Spo_2] ≤90% when breathing room air or <80 mm Hg when breathing 15 L/min of oxygen, plus either [1] a respiratory rate above 30/min or [2] clinical signs suggestive of intense respiratory muscle work and/or labored breathing) if it occurred within 7 days after surgical procedure.

INTERVENTIONS Patients were randomly assigned to receive standard oxygen therapy (up to 15 L/min to maintain Spo_2 of 94% or higher) (n = 145) or NIV delivered via facial mask (inspiratory pressure support level, 5-15 cm H_2O; positive end-expiratory pressure, 5-10 cm H_2O; fraction of inspired oxygen titrated to maintain Spo_2 ≥94%) (n = 148).

MAIN OUTCOMES AND MEASURES The primary outcome was tracheal reintubation for any cause within 7 days of randomization. Secondary outcomes were gas exchange, invasive ventilation–free days at day 30, health care–associated infections, and 90-day mortality.

RESULTS Among the 293 patients (mean age, 63.4 [SD, 13.8] years; n=224 men) included in the intention-to-treat analysis, reintubation occurred in 49 of 148 (33.1%) in the NIV group and in 66 of 145 (45.5%) in the standard oxygen therapy group within+ 7 days after randomization (absolute difference, −12.4%; 95% CI, −23.5% to −1.3%; *P* = .03). Noninvasive ventilation was associated with significantly more invasive ventilation–free days compared with standard oxygen therapy (25.4 vs 23.2 days; absolute difference, −2.2 days; 95% CI, −0.1 to 4.6 days; *P* = .04), while fewer patients developed health care–associated infections (43/137 [31.4%] vs 63/128 [49.2%]; absolute difference, −17.8%; 95% CI, −30.2% to −5.4%; *P* = .003). At 90 days, 22 of 148 patients (14.9%) in the NIV group and 31 of 144 (21.5%) in the standard oxygen therapy group had died (absolute difference, −6.5%; 95% CI, −16.0% to 3.0%; *P* = .15). There were no significant differences in gas exchange.

CONCLUSIONS AND RELEVANCE Among patients with hypoxemic respiratory failure following abdominal surgery, use of NIV compared with standard oxygen therapy reduced the risk of tracheal reintubation within 7 days. These findings support use of NIV in this setting.

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Postoperative acute respiratory failure is a major contributor to the overall risk of surgery, leading to an increase in morbidity and mortality.[1-3] The early postoperative period following abdominal surgery is associated with diaphragmatic dysfunction and a decrease in lung vital capacity, which may lead to atelectasis formation and hypoxemia.[4] Treating postoperative acute respiratory failure usually refers to tracheal reintubation and invasive mechanical ventilation.[5] Tracheal reintubation for acute respiratory failure is associated with higher mortality and increased health care utilization, with a longer duration of both intensive care unit (ICU) and hospital stay.[3] Reasons for the increase in mortality include complications during the reintubation period[6,7] and health care–associated infections such as pneumonia.[6-9] This suggests that postoperative outcome may be improved by strategies aimed at avoiding reintubation and invasive mechanical ventilation.[10]

Noninvasive ventilation (NIV) has proven effective in nonsurgical cases of acute exacerbation of chronic obstructive pulmonary disease[11] and cardiogenic pulmonary edema.[12] However, to date, no evidence supports the use of NIV in surgical patients with hypoxemic acute respiratory failure after abdominal surgery. Indeed, NIV is sometimes considered a relative contraindication after recent upper gastrointestinal tract surgery.[13]

To our knowledge, no multicenter randomized clinical trials have evaluated whether NIV could reduce the need for invasive mechanical ventilation and its effect on the incidence of health care–associated infections in patients who develop hypoxemic acute respiratory failure after abdominal surgery.[14,15]

We hypothesized that application of NIV may prevent reintubation and invasive mechanical ventilation and may decrease the rate of health care–associated infections.

We thus conducted a multicenter randomized clinical trial of NIV in surgical patients who developed hypoxemic acute respiratory failure after abdominal surgery, comparing NIV against standard oxygen therapy.

Methods

Trial Design and Oversight

The trial was an investigator-initiated, multicenter, stratified, parallel-group trial with a computer-generated allocation sequence and an electronic system-based randomization. The study protocol and statistical analysis plan (Supplement 2 and Supplement 3) were approved for all centers by a central ethics committee in accordance with French law. The trial was conducted in accordance with the Declaration of Helsinki. Written informed consent from the patient or consent from a relative was obtained on study inclusion. An independent data and safety monitoring committee oversaw the study conduct and reviewed blinded safety data, with interim analyses performed after the inclusion of 100 and 200 patients. Patients were screened and underwent randomization between May 2013 and September 2014 at 20 French ICUs. Randomization was performed centrally by the minimization method with the use of a computer-generated and blinded assignment sequence. Randomization was stratified according to study site, age (<60 vs ≥60 years), site of surgery (upper vs lower abdominal), and use of postoperative epidural analgesia, as this may influence outcomes.[16]

Patients

Patients were eligible for participation in the study if they were older than 18 years and had undergone laparoscopic or nonlaparoscopic elective or nonelective abdominal surgery under general anesthesia. Patients were included if they met the following criteria: a diagnosis of acute respiratory failure occurring within 7 days of the surgical procedure,[17,18] defined as the presence and persistence for more than 30 minutes of hypoxemia (defined by a partial oxygen pressure <60 mm Hg when breathing room air or <80 mm Hg when breathing 15 L/min of oxygen or a peripheral oxygen saturation [Spo_2] ≤90% when breathing room air plus either [1] a respiratory rate higher than 30/min or [2] clinical signs suggestive of intense respiratory muscle work and/or labored breathing, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retraction). Exclusion criteria were withholding of life-sustaining treatment,[19] contraindications to noninvasive ventilation, sleep apnea syndrome, immediate tracheal intubation, requirement for an emergent surgical procedure, and previous recruitment in another trial.

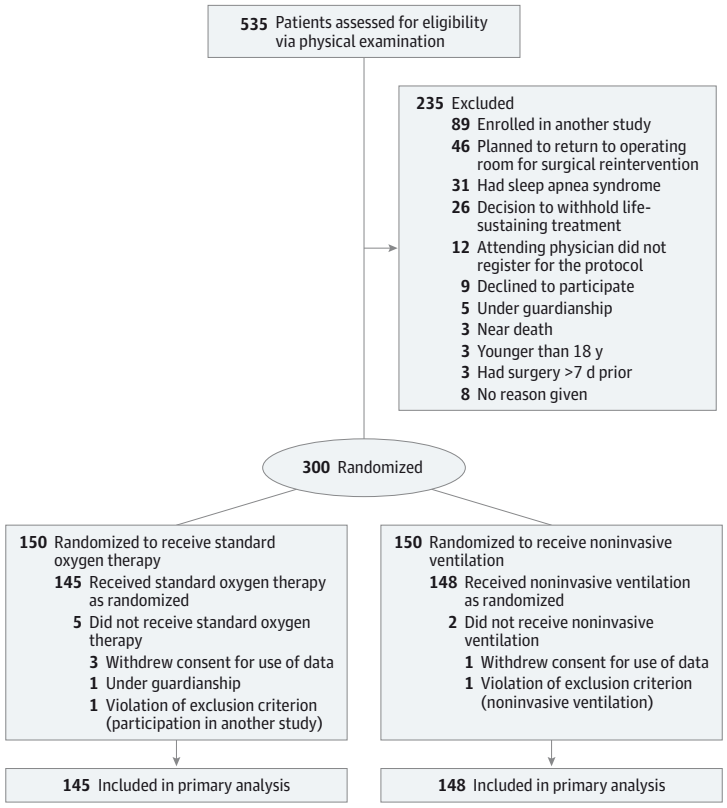
Causes of Acute Respiratory Failure

We assigned causes of acute respiratory failure following extubation using adapted published definitions[11,20-23] as follows: upper airway obstruction, aspiration or excess respiratory secretions, encephalopathy, congestive heart failure, pneumonia, and atelectasis.

Study Interventions

Patients were randomly assigned to receive either NIV or standard oxygen therapy alone from randomization until day 30 or ICU discharge, whichever came first. Patients assigned to standard oxygen therapy received supplemental oxygen at a rate of up to 15 L/min to maintain an Spo_2 of at least 94%. In the intervention group, NIV was delivered through a face mask connected to an ICU- or NIV-dedicated ventilator, using either a heated humidifier or heat and moisture exchanger to warm and humidify inspired gases.[24] Noninvasive ventilation was started at an inspiratory positive airway pressure of 5 cm H_2O, increasing to a maximum inspiratory pressure of 15 cm H_2O, aiming to achieve an expiratory tidal volume between 6 and 8 mL/kg of predicted body weight and a respiratory rate lower than 25/min. Positive end-expiratory airway pressure (PEEP) was started at 5 cm H_2O and increased as needed to a maximum of 10 cm H_2O.[4,10] PEEP and inspired oxygen fraction were titrated to maintain an Spo_2 of at least 94%. Ventilator settings were subsequently adjusted as needed for patient comfort.[4] Patients in this group were encouraged to use NIV for at least 6 hours, continuously or intermittently, during the first 24 hours after randomization. Between NIV sessions, patients received standard oxygen therapy as described above.

Figure 1. Enrollment, Randomization, and Follow-up of Participants in the Noninvasive Ventilation for Postextubation Respiratory Failure After Abdominal Surgery Study



The use of high-flow oxygen nasal cannulas was not permitted in either group. Any decision to discontinue NIV was left to the attending physician. All other aspects of patient care in both groups were conducted according to each center's routine clinical practice.

Criteria for Reintubation

To reduce the risk of delayed reintubation and to ensure consistency of indications for reintubation among all trial sites, predefined criteria were applied. Immediate reintubation was performed if patients had any of the following predefined major clinical events: respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, massive aspiration, persistent inability to clear respiratory secretions, heart rate of less than 50/min with loss of alertness, and severe hemodynamic instability without response to fluid and vasoactive drugs. After reintubation, all patients underwent ventilation with the same ventilation protocol, using a low-tidal-volume protective ventilatory strategy.[25]

Study Outcomes

The primary outcome for comparing NIV and standard oxygen therapy was any cause of reintubation within 7 days following randomization. Causes and time to reintubation were recorded. Secondary outcomes included gas exchange, health care-associated infection rate within 30 days, number of ventilator-free days (ie, days alive and without invasive mechanical ventilation) between days 1 and 30, antibiotic use duration, ICU and in-hospital length of stay, and 30- and 90-day mortality. Five of 7 secondary outcomes are reported in this article. Definitions for each health care-associated infection (pneumonia, urinary tract infection, central venous catheter-related infection, bacteremia, and surgical site infection, occurring both at least 48 hours after ICU admission and after study entry) are detailed in eAppendix 2 in Supplement 1.

Statistical Analysis

We estimated that with a sample of 150 patients per group evaluated for the primary efficacy outcome, the study had at least 90% power to determine superiority of noninvasive ventilation compared with standard oxygen therapy. For the intention-to-treat analysis, the following assumptions were made: a 65% event rate in the standard oxygen therapy group[10,26,27] and a 40% event rate in the noninvasive ventilation group[14,28,29] (absolute risk reduction with NIV of at least 25% based on expert opinion). Further assumptions (15% of included patients) were made relating to patients randomized despite not being eligible for randomization according to inclusion/exclusion criteria and loss to follow-up for the primary end point. Two interim analyses were conducted after the first 100 and 200 patient randomizations by an independent data and safety monitoring committee for early stopping of the study for safety (mortality within 90 days) using

Table 1. Patient Characteristics and Biomechanical Variables According to Study Group at Randomization

Characteristics	Standard Oxygen Therapy (n = 145)	Noninvasive Ventilation (n = 148)
Age, y		
Mean (SD)	64.4 (13.1)	62.5 (14.5)
≥60, No. (%)	89/145 (61.4)	92/148 (62.2)
Male, No. (%)	108/145 (74.5)	116/148 (78.4)
Body mass index[a]		
Mean (SD)	27.1 (6.2)	27.2 (5.9)
>30, No. (%)	34/143 (23.8)	42/147 (28.6)
Simplified Acute Physiology Score II at study entry, mean (SD)[b]	33.4 (11.7)	33.6 (12.8)
Sequential Organ Failure Assessment score at study entry, mean (SD)[c]	4.5 (2.7)	4.3 (2.6)
Preexisting conditions, No. (%)		
Current smoker	37/138 (26.8)	44/141 (31.2)
Alcohol abuse	26/142 (18.3)	23/141 (16.3)
Psychotropic use	16/144 (11.1)	15/147 (10.2)
Chronic hypertension	72/145 (49.7)	69/148 (46.6)
Ischemic heart disease	16/145 (11.0)	25/147 (17.0)
Chronic heart failure	4/143 (2.8)	7/146 (4.8)
Chronic obstructive pulmonary disease	18/143 (12.6)	29/148 (19.6)
Chronic kidney disease	9/145 (6.2)	5/147 (3.4)
Cirrhosis	26/145 (17.9)	23/147 (15.6)
Cancer	73/144 (50.7)	68/144 (47.2)
Sepsis	32/144 (22.2)	36/144 (25.0)
Clinical variables, mean (SD)		
Body temperature, °C	37.3 (0.8)	37.3 (0.8)
Heart rate, /min	103.2 (19.6)	102.2 (18.6)
Respiratory rate, /min	28.8 (7.3)	28.2 (7.7)
Blood pressure, mm Hg		
Systolic	135.6 (22.3)	132.8 (23.2)
Diastolic	68.7 (13.8)	70.1 (13.7)
Biochemical variables, mean (SD)		
Hemoglobin, g/dL	10.7 (1.9)	11.0 (2.2)
Hematocrit, %	31.7 (5.7)	32.5 (6.4)
White blood cell count, $\times 10^3/\mu L$	13.2 (6.8)	13.8 (9.3)

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

[b] The Simplified Acute Physiology Score II is based on 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease.

[c] The score on the Sequential Organ Failure Assessment includes subscores ranging from 0 to 4 for each of 5 components (circulation, lungs, liver, kidneys, and coagulation). Aggregated scores range from 0 to 20, with higher scores indicating more severe organ failure.

a prespecified Haybittle-Peto efficacy boundary[30] (α = .001 for the 2 interim analyses). A secondary modified intention-to-treat analysis was performed for the primary outcome including only patients who did not return to the operating room for reintervention. Unadjusted χ^2 testing was used for primary outcome analysis. Multiple imputation was additionally performed if the frequency of missing data was greater than 5%. A Markov chain Monte Carlo method was used for the multiple imputation procedure; we generated m = 5 complete data sets. Multiple logistic regression analysis was used to identify relevant baseline covariates associated with the primary outcome. Variables tested in the model were selected if $P<.15$ and then presented as absolute difference for binary variables and mean differences for continuous variables with 95% confidence intervals. Kaplan-Meier curves for reintubation and for mortality rates were plotted for the first 30 and 90 days, respectively, after inclusion in the study and were compared by the log-rank test. We compared the primary outcome in prespecified subgroups defined by stratification criteria according to age (<60 vs ≥60 years), site of surgery (upper vs lower abdominal), and use/nonuse of epidural analgesia. A 2-tailed $P<.05$ was considered to indicate statistical significance. SAS software, version 9.3 (SAS Institute Inc), was used for all analyses.

Results

Study Patients

From May 2013 through September 2014, 535 patients with acute respiratory failure within 7 days following abdominal surgery were eligible, of whom 300 underwent randomization, 150 to standard oxygen therapy and 150 to NIV (**Figure 1**). Seven patients were excluded after randomization because of withdrawn consent (n = 4) or ineligibility (n = 3). Data on the primary outcome were available for all 293 remaining patients (mean age, 63.4 [SD, 13.8] years; n = 224 men). Groups were similar with respect to inclusion, site, duration of surgery,

Table 2. Surgery and Acute Respiratory Failure Characteristics at Randomization

Characteristics	Standard Oxygen Therapy (n = 145)	Noninvasive Ventilation (n = 148)
Surgery		
Recent surgical history, No. (%)		
Elective	75/145 (51.7)	77/148 (52.0)
Emergency	70/145 (48.3)	71/148 (48.0)
Upper abdominal surgery, No. (%)	91/145 (62.8)	93/148 (62.8)
Type of surgery, No. (%)		
Liver resection	39/143 (27.3)	40/140 (28.6)
Colorectal resection	38/143 (26.6)	30/140 (21.4)
Gastrectomy	18/143 (12.6)	16/140 (11.4)
Esophagectomy	9/143 (6.3)	14/140 (10.0)
Pancreaticoduodenectomy	13/143 (9.1)	11/140 (7.9)
Other procedures	26/143 (18.2)	29/140 (20.7)
Laparotomy surgery, No. (%)	131/144 (91.0)	134/146 (91.8)
Vertical midline incision	87/137 (63.5)	82/139 (59.0)
Transverse incision	43/137 (31.4)	48/139 (34.5)
Other	7/137 (5.1)	9/139 (6.5)
Laparoscopic surgery, No. (%)	16/144 (11.1)	16/145 (11.0)
Thoracotomy/laparotomy, No. (%)[a]	3/143 (2.1)	7/143 (4.9)
Epidural analgesia, No. (%)	21/145 (14.5)	23/148 (15.5)
Duration of surgical procedure, mean (SD), h	4.3 (2.7)	4.1 (2.6)
Extubated <6 h after end of surgery, No. (%)	90/145 (62.1)	94/148 (63.5)
Acute respiratory failure		
Respiratory rate, mean (SD), /min	29 (7)	28 (8)
Time from end of surgery to acute respiratory failure, mean (SD), d	2.6 (1.7)	2.4 (1.6)
Time from extubation to acute respiratory failure, mean (SD), d	1.9 (1.6)	2.0 (1.6)
Time from acute respiratory failure to inclusion in study, median (IQR), h	3.1 (1.0-8.7)	2.8 (1.0-7.3)
Causes of acute respiratory failure, No. (%)[b]		
Atelectasis[c]	94/143 (65.7)	93/148 (62.8)
Tracheal secretions	54/143 (37.8)	58/148 (39.1)
Pneumonia	36/143 (25.2)	27/148 (18.2)
Pulmonary edema	23/143 (16.1)	21/148 (14.2)
Pleural effusion	19/143 (13.3)	18/148 (12.2)
Pulmonary embolism	11/143 (7.7)	6/148 (4.1)
Arterial blood gas at randomization, mean (SD)		
pH	7.41 (0.07)	7.42 (0.07)
Pao_2:FIO_2 ratio, mm Hg	188 (71)	201 (69)
$Paco_2$, mm Hg	37 (7)	39 (7)
HCO_3, mmol/L	24 (4)	25 (4)

Abbreviations: FIO_2, fraction of inspired oxygen; IQR, interquartile range.

[a] In these patients, 2 incisions were made to perform the surgery, one through the abdomen and one through the thorax.

[b] Causes of acute respiratory failure may be multiple.

[c] Atelectasis was defined as lung opacification with shift of the mediastinum, hilum, or hemidiaphragm toward the affected area and compensatory overinflation in the adjacent nonatelectatic lung.

causes of acute respiratory failure, time from surgery, time from extubation to acute respiratory failure (**Table 1** and **Table 2**), and gas exchange (Table 2 and eTable 1 in Supplement 1). The initial settings were as follows: for the standard oxygen therapy group, mean oxygen flow was 10.4 L/min (SD, 5.1 L/min); for the NIV group, mean inspiratory pressure was 6.7 cm H_2O (SD, 2.9 cm H_2O), mean PEEP was 5.4 cm H_2O (SD, 1.3 cm H_2O), and mean fraction of inspired oxygen was 50% (SD, 16%), resulting in a mean tidal volume of 8.3 mL/kg (SD, 3.1 mL/kg) of predicted body weight (eTable 2 in Supplement 1).

Outcomes

Primary Outcome

Noninvasive ventilation improved the primary outcome of the 293 patients included in the intention-to-treat analysis; reintubation occurred in 49 of 148 patients (33.1%) in the NIV group and 66 of 145 (45.5%) in the standard oxygen therapy group at 7 days after randomization (absolute difference, −12.4%; 95% CI, −23.5% to −1.3%; $P = .03$) (**Table 3**, **Figure 2**, and the eFigure in Supplement 1). The multivariable analysis is shown in eTable 3 in Supplement 1, and NIV was signifi-

Table 3. Primary and Secondary Outcomes According to Study Group

Variables	Standard Oxygen Therapy (n = 145)	Noninvasive Ventilation (n = 148)	Absolute Difference (Noninvasive Ventilation – Standard Oxygen Therapy), % (95% CI)	*P* Value
Outcomes, No./Total (%)				
Primary outcome: reintubation to day 7	66/145 (45.5)	49/148 (33.1)	−12.41 (−23.51 to −1.31)	.03
Secondary outcomes[a]				
Reintubation to day 30	72/145 (49.7)	57/148 (38.5)	−11.14 (−22.44 to 0.16)	.06
Overall health care-associated infections to day 7	44/145 (30.3)	27/148 (18.2)	−12.1 (−22.52 to −1.69)	.02
Pneumonia to day 7	32/145 (22.1)	15/148 (10.1)	−11.93 (−20.94 to −2.93)	.005
Overall health care-associated infections to day 30	63/128 (49.2)	43/137 (31.4)	−17.83 (−30.22 to −5.44)	.003
Pneumonia to day 30	38/128 (29.7)	20/137 (14.6)	−15.09 (−25.72 to −4.45)	.003
30-Day mortality	22/144 (15.3)	15/148 (10.1)	−5.04 (−13.32 to 3.24)	.20
90-Day mortality	31/144 (21.5)	22/148 (14.9)	−6.51 (−15.99 to 2.96)	.15
90-Day mortality in intubated patients	29/72 (40.3)	18/57 (31.6)	−8.8 (−17.29 to 4.12)	.31
Service Utilization, Median (IQR)				
Days of invasive mechanical ventilation over 30 d	0 (0-5) [n=145]	0 (0-3) [n=148]	−0.93 (−2.51 to 0.64)[b]	.05
Invasive ventilation-free days to day 30[c]	30 (21.4-30) [n=145]	30 (25.9-30) [n=148]	2.22 (−0.11 to 4.55)[d]	.04
Invasive ventilation-free days to day 30 with deceased accounting for 0 d[c]	30 (20.8-30) [n=145]	30 (25.9-30) [n=148]	2.30 (−0.33 to 4.93)[d]	.04
Days in ICU to day 30	8 (5-15) [n=144]	7 (5-14) [n=146]	−0.06 (−1.99 to 1.87)	.80
Days in ICU to day 90	8 (5-15) [n=143]	7 (5-14) [n=146]	0.18 (−3.08 to 3.44)	.45
Overall days in hospital to day 90	25 (15-39) [n=130]	22 (14-35.5) [n=140]	−2.39 (−7.68 to 2.91)	.19
Days in hospital to day 90 (survivors only)	27 (16-43.5) [n=108]	20.5 (14-32) [n=114]	−5.21 (−11.03 to 0.62)[d]	.02
Time from inclusion to reintubation, h	24 (0-72) [n=72]	48 (24-120) [n=57]	11.67 (−15.64 to 51.27)	.31
Time from extubation to reintubation, d	3 (2-5) [n=72]	4 (2-7.3) [n=60]	0.59 (−0.86 to 2.04)	.14
Time from acute respiratory failure to reintubation, d	1 (1-3) [n=72]	2 (1-6) [n=57]	0.66 (−0.76 to 2.09)	.08

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] For additional data on secondary outcomes, see eTables 2, 3, 5, and 6 in Supplement 1.

[b] Log: −0.13% (95% CI, −0.49% to 0.22%).

[c] The number of invasive ventilation–free days was defined as the number of days without invasive mechanical ventilation at day 30.

[d] Because of nonnormal distribution of some continuous variables, a nonparametric analysis was used to compare groups, but the 95% CI of the mean difference may cross 0.

cantly associated with reduced reintubation. Time from inclusion to reintubation (Table 3) and reasons for reintubation (eTable 4 in Supplement 1) did not significantly differ between the groups.

No significant difference was observed in the number of patients requiring reintubation for reoperation (16/148 [10.8%] in the NIV group and 16/145 [11%] in the standard oxygen therapy group; *P* = .95).

In the modified intention-to-treat analysis including all patients except those reintubated for reoperation (n = 261), NIV also improved the primary outcome. Reintubation occurred in 33 of 132 patients (25.0%) in the NIV group and 50 of 129 patients (38.8%) in the standard oxygen therapy group (*P* = .02).

Secondary Outcomes

Among patients subsequently reintubated, patients who received NIV spent less time under invasive mechanical ventilation than patients treated with standard oxygen therapy alone (Table 3). There were no significant differences in gas exchange between groups (eTable 1 in Supplement 1).

At 30 days, compared with standard oxygen therapy, NIV was associated with significantly more ventilator-free days (25.4 vs 23.2 days; absolute difference, −2.2 days; 95% CI, −0.1 to 4.6 days; *P* = .04). Patients treated with NIV also experienced significantly fewer health care-associated infections (43/137 patients [31.4%] vs 63/128 [49.2%]; absolute difference, −17.8%; 95% CI, −30.2% to −5.4%; *P* = .003), especially less ICU-acquired pneumonia (20/137 patients [14.6%] vs 38/128 [29.7%]; *P* = .003) (Table 3 and eTable 5 in Supplement 1). Microorganisms causing pneumonia are detailed in eTable 6 in Supplement 1. At 90 days, 22 of 148 patients (14.9%) in the NIV group and 31 of 144 (21.5%) in the standard oxygen therapy group had died (absolute difference, −6.5%; 95% CI, −16.0% to 3.0%; *P* = .15) (Table 3 and **Figure 3**).

Clinical Tolerance

No significant difference was seen between the 2 groups in the overall incidence of serious adverse events (eTable 2 in Supplement 1). Seven patients received NIV as rescue therapy

in the standard oxygen therapy group, of whom 3 (42.9%) were subsequently intubated. There were 3 episodes of cardiac arrest, 2 occurring before intubation (1 in the standard oxygen therapy group and 1 in the NIV group). Tolerance and adverse effects of NIV after the first trial in the NIV group are reported in eTable 2 in Supplement 1.

Discussion

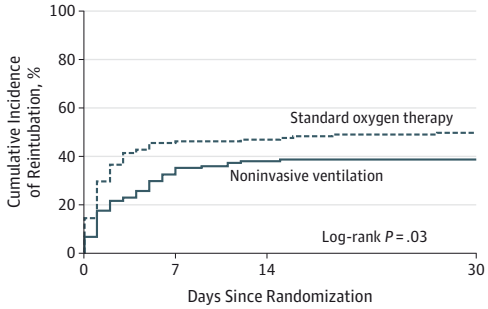
In this multicenter randomized clinical trial conducted among patients with hypoxemic acute respiratory failure after abdominal surgery, noninvasive ventilation delivered via face mask reduced the need for reintubation and for invasive mechanical ventilation and was associated with fewer episodes of health care-associated infection compared with standard oxygen therapy.

Hypoxemia develops in 30% to 50% of patients after abdominal surgery and can in some patients be well tolerated without symptoms.[4,22,28] In others, however, hypoxemia can progress to severe acute respiratory failure. The genesis of hypoxemic acute respiratory failure postoperatively is multifactorial and partly related to atelectasis due to hypoventilation and collapsed alveoli, retained secretions, and diaphragmatic dysfunction.[29,31] Atelectasis promotes bacterial growth and increases lung permeability, leading to pneumonia.[32] In our study, NIV significantly decreased overall health care-associated infections and halved the rate of pneumonia. Noninvasive ventilation can reverse loss of pulmonary volume through the combined positive effects of PEEP and inspiratory pressure support, which increase lung ventilation, reopen atelectatic alveoli, and improve gas exchange.[4] Reducing atelectasis by NIV could also decrease bacterial growth, thus mitigating bacterial translocation from the lung into the bloodstream.[32] Avoidance of endotracheal intubation, bypassing the upper airways, is probably the major reason for the pneumonia reduction observed in patients treated by NIV.[33] Moreover, NIV has been shown to reduce overall nosocomial infection rates through reduction in both the number and duration of invasive devices such as intravenous and bladder catheters.[33] Finally, reducing health care-associated infections, especially pneumonia, could contribute to the trend toward lower mortality observed in the NIV group (Table 3 and Figure 3).

Complications have been reported with NIV, such as gastric distention and pulmonary aspiration. Noninvasive ventilation may also potentially impede patients' ability to cough and expectorate postoperatively. In the present study, no adverse events were reported in either group. We did not observe higher morbidity and mortality in the NIV group, contrary to that reported in another postextubation study because of delayed reintubation in the NIV group.[20] The selection of appropriate postoperative patients who may benefit from postextubation NIV is a key factor.[4,34] One randomized clinical study by Squadrone et al[22] evaluated the use of noninvasive continuous positive airway pressure delivered via helmet after abdominal surgery. They studied 209 patients who developed hypoxemia immediately after extubation without necessarily having signs of respiratory distress. Nonetheless, their early use of noninvasive continuous positive airway pressure significantly decreased the incidence of reintubation from 10% to 1%. Our study presents several differences: (1) we evaluated the efficacy of NIV delivered with face mask using 2 levels of positive airway pressure and (2) NIV was used as a therapeutic application in a more severe patient cohort with hypoxemic acute respiratory failure and not prophylactically in patients with hypoxemia alone. As a result, the respective incidence of reintubation (standard oxygen therapy control group rate of 10% for the study by Squadrone et al vs 45.5% in the current study) and mortality (3% in the control group of the study by Squadrone et al vs 22% in the current study) differed between the 2 studies (Table 3).

The strengths of the present study are its large sample size, the selected population base, multicenter design, the explicit criteria for reintubation, and a complete postoperative follow-up. Baseline characteristics in the 2 groups were well matched, and the criteria for health care-associated infection diagnosis are both validated and robust. The trial excluded patients who underwent another immediate surgical procedure, and stratification was performed according to study site, age, site of surgery, and use/nonuse of postoperative epidural analgesia.

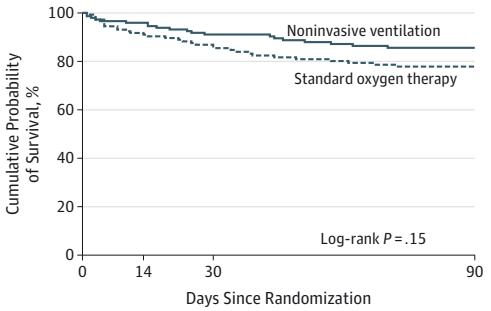
Figure 2. Cumulative Incidence of Reintubation Between Randomization and Day 30 According to Study Group



No. at risk

Standard oxygen therapy	145	79	76	71
Noninvasive ventilation	148	99	90	87

Figure 3. Probability of Survival Between Randomization and Day 90 According to Study Group



No. at risk

Standard oxygen therapy	145	132	125	102
Noninvasive ventilation	148	141	131	109

Our study has several limitations. First, the observed rate of reintubation in our study was lower than predicted in the standard oxygen therapy group.[2,3,17,35] This could be due, in part, to exclusion of patients in whom acute respiratory failure was an early symptom of surgical complications needing immediate reintervention. Although invasive endotracheal mechanical ventilation has remained the cornerstone of ventilatory strategy for severe acute respiratory failure for many years,[2] several studies have shown that mortality associated with pulmonary complications is largely related to the risks of postoperative reintubation and mechanical ventilation.[2,3,36-38] Second, the present study was not designed to show a significant decrease in mortality in the NIV group. The lack of significance for lower mortality observed in the NIV group (from 22% to 15% at day 90) could be due to an underpowered design. The low mortality rate in the NIV group may result from the cumulative effects of a decreased reintubation rate, a shorter duration of invasive mechanical ventilation, and a reduced rate of health care–associated infections, especially pneumonia (Table 3). Third, although we applied predefined criteria for reintubation, bias cannot be completely ruled out because blinding with NIV was not feasible. Fourth, the clinically relevant effect size used in the power analysis was 25%. Because we were not able to identify randomized clinical trials that included similar patients, this was based on expert opinion and was chosen to limit the likelihood of a type 1 error.

Recent high-impact trials have demonstrated the benefits in nonsurgical hypoxemic respiratory failure[21] or equivalence of high-flow nasal cannula compared with NIV in patients after cardiothoracic surgery with moderate to severe hypoxemia.[23] Future studies comparing use of high-flow oxygen cannula vs standard oxygen therapy and NIV for patients after abdominal surgery as preventive (prophylactic)[39] or curative application are needed.[40]

Conclusions

Among patients with hypoxemic respiratory failure following abdominal surgery, use of NIV compared with standard oxygen therapy reduced the risk of tracheal reintubation within 7 days. These findings support use of NIV in this setting.

ARTICLE INFORMATION

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Author Contributions: Dr Molinari 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.
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Acquisition, analysis, or interpretation of data: Jaber, Lescot, Futier, Paugam-Burtz, Seguin, Ferrandiere, Lasocki, Mimoz, Hengy, Sannini, Pottecher, Abback, Riu-Poulenc, Constantin, Masseret, Beaussier, Verzilli, De Jong, Chanques, Brochard, Molinari.
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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. List of NIVAS Trial Investigators

Independent Data and Safety Monitoring Committee: K. Asehnoune, CHU Nantes, France; X. Capdevila, CHU Montpellier, France; E. Marret, Tenon Hospital, Paris, France.

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eAppendix 2. Supplemental Methods

Study oversight

The Non-Invasive Ventilation after Abdominal Surgery (NIVAS) was an investigator-initiated, multi-center, stratified, two-arm parallel-group trial with a computer-generated allocation sequence and an electronic system-based randomization. The study protocol and statistical analysis plan were approved for all centers by a central Ethics Committee (Comité de Protection des Personnes Sud Mediterranée III, Nimes, France) according to French law. The NIVAS study was conducted in accordance with the declaration of Helsinki and was registered at http://www.clinicaltrials.gov with trial identification number NCT01971892. Depending on the severity of the illness and competency, informed written or witnessed oral consent from the patient, or witnessed consent from a relative, was obtained upon study inclusion. Whenever possible, written consent for continued participation in the trial was obtained from the patient in the subsequent 7 days.

An independent data and safety monitoring committee oversaw the study conduct and reviewed blinded safety data, with interim analyses performed after the inclusion of 100 and 200 patients. The steering committee vouched for the accuracy and completeness of the data and analysis, and the fidelity of the study to the protocol, and took the decision to submit the manuscript for publication. The writing committee wrote all drafts of the manuscript without editorial assistance; all the authors provided revisions and comments. There was no industry support or involvement in the trial. Patients were screened and underwent randomization between May 2013 and September 2014 at 20 ICUs in 17 French university and 3 non-university hospitals. All sites had a long experience with NIV (more than 10 years of NIV use for ARF, and more than 5 years of NIV use for ARF following abdominal surgery). Randomization was performed centrally, with the use of a computer-generated and blinded assignment sequence. Randomization was stratified according to study site, age (less or more than 60 years), site of surgery (upper or lower abdominal) and according to the use of postoperative epidural analgesia, which may influence outcomes. Treatment assignments were concealed from research staff, the statistician and the data monitoring/safety committee.

Patients

Inclusion criteria

1. Adult patients older than 18 years
2. Laparoscopic or non-laparoscopic elective or non-elective abdominal surgery under general anesthesia
3. Acute respiratory failure occurring within 7 days of the surgical procedure, defined as presence and persistence > 30 minutes of at least one of the two following:

   1) a respiratory rate above 30 breaths/min and

   2) clinical signs suggesting respiratory muscle fatigue, labored breathing, or both, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retractions and

   3) hypoxemia defined by a partial oxygen pressure lower than 60 mmHg when breathing room air, or lower than 80 mmHg with 15 liters per minute of oxygen or a peripheral oxygen saturation of ≤90% breathing room air (PaO_2/FIO_2≤300 mmHg).
4. And informed consent obtained
5. And valid affiliation to the Social Security System

Exclusion criteria

1. Limitation of therapy
2. Contraindications to noninvasive ventilation: required immediate tracheal intubation and invasive mechanical ventilation, hemodynamic instability defined by systolic arterial blood pressure below 90 mm Hg or mean arterial blood pressure below 65 mm Hg, use of vasopressors; a Glasgow Coma Scale score of 12 points or less (on a scale from 3 to 15, with lower scores indicating reduced levels of consciousness)
3. Required an emergent surgical procedure (operation that had to be performed within 12 hours after inclusion in the study)
4. Previous recruitment in another trial.
5. Pregnancy
6. Refusal to participate

Interventions and trial settings for NIVAS trial

Patients were randomly assigned to receive either NIV (NIV-group) or standard-oxygen

therapy alone (oxygen-group) from randomization until day 30 or ICU discharge, whichever came first. Patients assigned to standard-oxygen therapy received supplemental oxygen at a rate of up to 15 liters per minute in order to maintain peripheral oxygen saturation ≥94%. In the intervention group (NIV-group), NIV was delivered through a face mask connected to an ICU or NIV-dedicated ventilator, using either heated humidifier or heat and moisture exchanger to warm and humidify inspired gases. NIV was started at an inspiratory positive airway pressure of 5 cm of water and was increased to a maximum inspiratory pressure of 15 cm of water aiming to achieve an expiratory tidal volume between 6 to 8 ml per kilogram of predicted body weight and a respiratory rate of less than 25 breaths per minute. Positive-end expiratory airway pressure (PEEP) was started at 5 cm of water and was increased to a maximum of 10 cm of water. PEEP and inspired oxygen fraction were titrated to maintain an arterial oxygen saturation ≥94%. Ventilator settings were subsequently adjusted as needed for patient comfort. Patients in this group were encouraged to use NIV for at least 6 hours, continuously or fractioned, during the first 24 hours after randomization. Between NIV sessions, patients received standard-oxygen therapy as described above. The use of high-flow oxygen nasal cannulae (>15 liters per minute) was not permitted in either group. The decision regarding when to discontinue NIV was left to the attending physician. Participants who did not receive the assigned treatment or who did not adhere to the protocol were followed up in full, and their data were included in the analysis according to the intention-to-treat principle (see statistical analysis section). All other aspects of patient care in both groups were conducted according to each center's routine clinical practice.

Criteria of endotracheal intubation

To reduce the risk of delayed re-intubation and to ensure the consistency of indications for re-intubation between all trial sites, predefined criteria were applied in all participating centers. In the two groups, immediate re-intubation was performed if the patients met any of the following predefined major clinical events: respiratory or cardiac arrest; respiratory pauses with loss of consciousness or gasping for air; massive aspiration; persistent inability to clear respiratory secretions; heart rate below 50 beats per min with loss of alertness; and severe hemodynamic instability without response to fluids

and vasoactive drugs. After re-intubation, all patients were ventilated with the same ventilation protocol, according to the low-tidal-volume protective ventilatory strategy.

Data collection and definitions

Causes of acute respiratory failure (ARF)

We assigned causes of ARF following extubation, with adapted published definitions: upper-airway obstruction; aspiration or excess respiratory secretions; severe encephalopathy; congestive heart failure; pneumonia and atelectasis. Severe encephalopathy was defined by Glasgow coma scale of 12 points or less (on a scale from 3 to 15, with lower scores indicating reduced levels of consciousness).

Atelectasis was defined as lung opacification with shift of the mediastinum, hilum or hemi-diaphragm towards the affected area and compensatory overinflation in the adjacent non-atelectatic lung.

Health-Care associated infections

Diagnostic criteria for health-care associated infections were adapted from CDC criteria. The sites and dates of diagnosis of all healthcare associated infections were recorded as well as antibiotic regimens given during the ICU stay within 30 days after inclusion in the study.

Pneumonia, urinary tract infection, central venous catheter-related infection, bacteremia and surgical-site infection, occurring both at least 48 hours after ICU admission and after inclusion in the study were collected according to the following definitions.

Pneumonia was suspected in patients with a combination of new and persistent lung infiltrates on chest X-ray, a temperature greater than 38°C, and macroscopically purulent tracheal secretions while receiving either standard oxygen therapy, noninvasive ventilation or invasive mechanical ventilation. Pneumonia was ascertained by the positivity of a quantitative respiratory culture, defined as at least 1 microorganism recovered at concentration of at least 1000 colony forming units per mL for blinded protected telescoping catheter, of at least 10000 colony forming units per mL for broncho-alveolar lavage and of at least 1000000 colony forming units per mL for tracheal aspirates. In patients clinically suspected of having pneumonia but treated with noninvasive ventilation, the positivity of a blinded protected telescoping catheter culture at the same significant threshold, when available, or the sole administration of new

antibiotics in the absence of other sites of infection was used to characterize the presence of pneumonia.

The modified Clinical Pulmonary Infection Score (CPIS) at suspected pneumonia was calculated from the first five variables (see table CPIS). The CPIS gram/culture was calculated from the CPIS score by adding two more points when gram stains or culture were positive. A score of more than six at baseline or after incorporating the gram stains (CPIS gram) or culture (CPIS culture) results was considered suggestive of pneumonia.

The Modified Clinical Pulmonary Infection Score (modified CPIS)

CPIS Points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature, °C	≥36.5 and ≤38.4	≥38.5. and ≤38.9	≥39 or ≤36.4
Leukocytes count, per mm^3	≥4,000 and ≤11,000	<4,000 or >11,000	<4,000 or >11,000 + band forms ≥500
P_{aO2}/F_{IO2}, mmHg	>240 or ARDS		≤240 and no evidence of ARDS
Microbiology	Negative		Positive

Urinary tract infection was defined by the association of fever (body temperature greater than 38°C) and a urine culture with no more than two species of organisms, at least one of which is a bacteria of at least 100000 colony forming units per ml, in patients with no other evident source of infection.

Catheter-related infection was defined as a combination of fever (body temperature greater than 38°C), a quantitative catheter-tip culture eluate in broth showing at least one microorganism in a concentration of at least 1000 colony forming units per mL, and resolution of fever within 48 h after catheter removal and without any change in antimicrobial therapy, and no other evident source of infection identified.

Primary bacteremia was defined as a combination of fever (body temperature greater than 38°C), at least 1 positive blood culture (two or more blood cultures drawn on separate occasions when coagulase-negative staphylococci were isolated) not related to an infection at another site.

Surgical-site infection diagnostic was performed according standard CDC definitions (Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999: Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250-78).

An independent infectious disease specialist reviewed all clinical and microbiological informations for each patient.

TABLE 1
CRITERIA FOR DEFINING A SURGICAL SITE INFECTION (SSI)*

Superficial Incisional SSI

Infection occurs within 30 days after the operation
and
infection involves only skin or subcutaneous tissue of the incision
and at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.[433]

Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
and
infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision
and at least *one* of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopatholog ic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/Space SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
and
infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation
and at least *one* of the following:

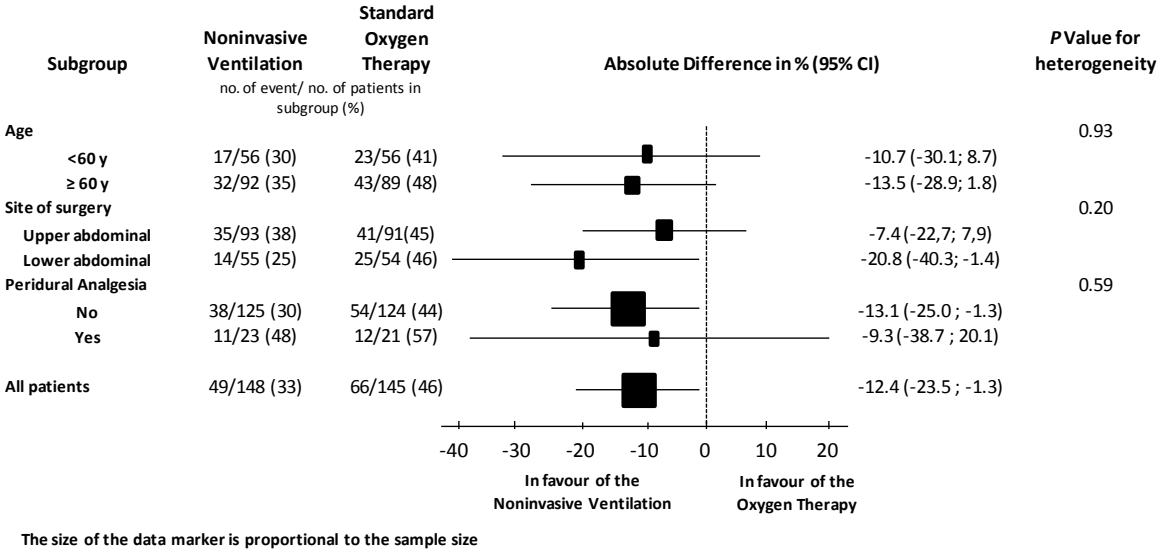
1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

* Horan TC et al.[22]
† National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.
‡ If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.

Definitions for outcomes

The primary outcome for comparing NIV and standard-oxygen therapy was any cause of re-intubation within 7 days following randomization. Causes and time to re-intubation were recorded. Secondary outcomes included gas exchange, healthcare associated infections rate within 30 days, the number of ventilator-free days (i.e. days alive and without invasive mechanical ventilation) between day-1 and day-30, antibiotic use duration and numbers, ICU and in-hospital lengths of stay, 30 and 90-day mortality.

eFigure. Absolute Difference of Intubation at 30 Days



The eFigure shows the absolute difference (black boxes) with 95% confidence intervals (horizontal lines) for the primary outcome measure of intubation by day 7 in the noninvasive ventilation group, as compared with the oxygen standard therapy group, among all the patients and in the predefined subgroups according the stratification variables (age less or more than 60 years, site of surgery upper or lower abdominal and use or not of postoperative epidural analgesia).

eTable 1. Gas Exchange According to Study Group

Variable	Standard Oxygen Therapy (N = 145)		Noninvasive Ventilation (N = 148)		*P* Value
	No. Assessed	Value	No. Assessed	Value	
pH					
Randomization	126	7.41±0.07	134	7.42±0.07	
Hour 1	119	7.41±0.08	114	7.42±0.07	.61
Day 1	99	7.41±0.09	90	7.42±0.07	.87
PaO_2:FiO_2, mm Hg					
Randomization	126	187.8±71.0	134	200.8±69.0	.
Hour 1	119	202.5±92.3	114	187.4±79.4	.33
Day 1	99	220.7±87.3	90	216.0±96.1	.60
$PaCO_2$, mm Hg					
Randomization	126	37.0±6.5	134	38.5±6.9	
Hour 1	119	38.6±7.9	114	38.5±6.9	.96
Day 1	99	39.0±7.1	90	39.3±8.0	.86
HCO_3^-, mmol/liter					
Randomization	126	23.6±3.8	134	24.9±3.8	
Hour 1	119	24.8±5.0	114	24.7±4.4	.58
Day 1	99	24.7±3.9	90	24.9±3.9	.66

Values are displayed as mean±SD.
FiO_2 denotes fraction of inspired oxygen, Partial pressure of arterial oxygen (PaO_2) and partial pressure of arterial carbon dioxide ($PaCO_2$) were measured in millimeters of mercury.
To estimated FiO_2, for spontaneously breathing non-intubated patients, each liter of oxygen was assumed to add 3% oxygen to room air.

e**Table 2.** Settings, Monitored Parameters, Tolerance and Side Effects of Noninvasive Ventilation

	Noninvasive Ventilation (N = 148)			
Variable	**All (N = 148)**	**Success NIV (N=99)**	**Failure NIV (N=49)**	***P* value**
NIV parameters				
Type of ventilator used ICU ventilator without NIV-option (double-line) ICU ventilator with NIV-option (double-line) Dedicated NIV ventilator (single-line)	 8 (6%) 100 (74%) 27 (20%)	 6 (7%) 63 (70%) 21 (23%)	 2 (5%) 37 (82%) 6 (13%)	.31
Gas conditioning device Heated humidifier Heated and Moisture Exchanger (Filter) None	 69 (51%) 62 (46%) 3 (2%)	 50 (55%) 38 (42%) 2 (2%)	 19 (43%) 24 (55%) 1 (2%)	
Settings parameters				
Pressure Support Level, cmH2O	6.7 ± 2.9	6.3 ± 3.0 (N=92)	7.5 ± 2.7 (N=47)	.02
PEEP level, cmH2O	5.4 ± 1.3	5.4 ± 1.3 (N=94)	5.4 ± 1.3 (N=47)	.99
Inspiratory trigger flow, L/min, median (IQR)	0.3 (0.3-1)	0.3 (0.3-1) (N=54)	0.3 (0.3-1) (N=31)	.17
Expiratory trigger	28.9 ± 9.1	27.9 ± 7.1 (N=54)	30.7 ± 11.8 (N=30)	.23
FiO_2, %	50.0 ± 15.9	48.3 ± 14.4 (N=96)	53.5 ± 18.1 (N=48)	.10
Monitored parameters				
Expiratory tidal volume, ml	559.3 ± 172.4	568.0 ± 172.2 (N=77)	542.5 ± 173.7 (N=40)	.52
Respiratory rate, breaths/min	24.2 ± 7.3	23.9 ± 7.1 (N=91)	24.8 ± 7.8 (N=44)	.73
Global evaluation by nurse of tolerance and side effects (Numeric Rating Scale: 0= no or minimal to 10= maximal) median (IQR)				
Leaks around the mask Category 0-2 – no (%)	2 (0-4) 78 (64)	1.5 (0-3) (N=82) 55 (67)	2 (0-4) (N=40) 23 (58)	.13
Dry mouth and/or nasal congestion Category 0-2 – no (%)	0 (0-2) 94 (78)	0 (0-2) (N=80) 64 (80)	0 (0-2.3) (N=40) 30 (75)	.69
Copious bronchial secretions Category 0-2 – no (%)	0 (0-3) 94 (78)	0 (0-2) (N=81) 64 (80)	0 (0-4.3) (N=40) 30 (75)	.07
Irritation ocular / conjunctivitis Category 0-2 – no (%)	0 (0-0) 86 (71)	0 (0-0) (N=81) 62 (76)	0 (0-0) (N=40) 24 (60)	.15
Skin ulcerations Category 0-2 – no (%)	0 (0-0) 115 (95)	0 (0-0) (N=82) 78 (95)	0 (0-0) (N=39) 37 (95)	.92
Gastric distension Category 0-2 – no (%)	0 (0-0) 110 (91)	0 (0-0) (N=81) 74 (91)	0 (0-0) (N=40) 36 (90)	.78
Anxiety Category 0-2 – no (%)	0 (0-5) 80 (66)	0 (0-4) (N=82) 57 (70)	2 (0-5.3) (N=40) 23 (58)	.15
Bronchial secretions No Moderate Excessive	 92 (74%) 24 (19%) 8 (7%)	 64 (77%) 13 (16%) 6 (7%)	 28 (68%) 11 (27%) 2 (5%)	.33
Duration of NIV delivered during the first 24h after inclusion, hours	7.4 ± 4.9	7.6 ± 4.8	7.2 ± 5.1	.72
Total duration of NIV use during ICU stay-days, median (IQR), d	4 (1-5)	4 (1-5)	1 (1-7)	.22
Number of patients who received at least 6h of NIV during the first 24h after inclusion, no. (%)	102 (68.9)	70 (70.7)	32 (65.3)	.50
Number of patients who received NIV during the entire period prior to primary outcome assessment, no. (%)	36 (24%)	20 (20%)	16 (33%)	.10

Data are displayed as number of patients or mean±SD. IQR, interquartile range
Data are obtained after the first session of NIV.
"Success NIV" was defined as clinical improvement leading to discharge to regular ward, while exitus or need for endotracheal reintubation was considered "failure NIV".

eTable 3. Bivariable and Multivariable Analysis of Factors Associated With the Primary Outcome

	Bivariable Analysis				Multivariable Analysis*	
Characteristic#	**Primary outcome (Re-intubation D7)**		**Odds ratio (95%CI)**	**P Value**	**Adjusted Odds ratio (95%CI)**	**P Value**
	No (N = 178)	**Yes (N = 115)**				
Randomization group						
Noninvasive Ventilation	99 (55.6)	49 (42.6)	0.59 (0.37-0.95)	.00	0.485 (0.228-0.816)	.0065
Standard Oxygen Therapy	79 (44.4)	66 (57.4)	reference			
Patient-specific risk factors						
Age – yr (n)	62.9±14.0 (178)	64.2±13.5 (115)	1.00 (0.99-1.02)	.42		
Age ≥ 60 (reference) - yr, n (%)	106/178 (59.6)	75/115 (65.2)	1.27 (0.78-2.07)	.33		
Male gender (reference: Female) – no. (%)	129/178 (72.5)	95/115 (82.6)	1.80 (1.01-3.23)	.046		
Body mass index – kg/m^2 (n)	27.7±5.9 (175)	26.9±6.3 (115)	1 (0,97-1,04)	.81		
Body mass index > 30 kg/m^2 (reference: <30) – no. (%)	44/175 (25.1)	32/115 (27.8)	1.17 (0.69-1.99)	.55		
Simplified Acute Physiology Score II > 40 at entry into the study (reference: <40) – no. (%) **	29/177 (16.4)	41/115 (35.7)	2.85 (1.64-4.94)	.0001	3.119 (1.718-5.665)	.0002
Sequential Organ Failure Assessment score at entry into the study (n) †	4.2±2.5 (169)	4.7±2.9 (113)	0,97 (0,88-1,05)	.43		
Preexisting conditions – no. (%)						
Current smoker (reference: No)	45/171 (26.3)	36/108 (33.3)	1.40 (0.83-2.37)	.21		
Alcohol abuse (reference: No)	28/171 (16.4)	21/111 (18.9)	1.19 (0.64-2.23)	.58		
Psychotropic use (reference: No)	15/178 (8.4)	16/113 (14.2)	1.79 (0.85-3.79)	.12		
Chronic arterial hypertension (reference: No)	88/178 (49.4)	53/113 (46.1)	0.87 (0.55-1.40)	.58		
Ischemic heart disease (reference: No)	27/178 (15.2)	14/114 (12.3)	0.78 (0.39-1.57)	.49		
Chronic heart failure (reference: No)	9/178 (5.1)	2/114 (1.8)	0.33 (0.07-1.58)	.21		
Chronic obstructive pulmonary disease (reference: No)	25/176 (14.2)	22/111 (19.8)	1.49 (0.79-2.80)	.21		
Chronic kidney disease (reference: No)	6/178 (3.4)	8/115 (7.0)	2.14 (0.72-6.35)	.16		
Liver cirrhosis(reference: No)	32/178 (18.0)	17/114 (14.9)	0.80 (0.42-1.52)	.49		
Cancer (reference: No)	83/175 (47.4)	58/113 (51.3)	1.17 (0.73-1.88)	.52		
Sepsis (reference: No)	42/175 (24.0)	26/113 (23.0)	0.95 (0.54-1.66)	.85		
Clinical variables						
Body temperature, ℃ (n) ‡	37.3±0.8 (167)	37.3±0.8 (100)	1,07 (0,8-1,44)	.64		
Heart rate - beats/min (n)	101±18 (178)	105±21 (112)	1.00 (0.99-1.01)	.67		
Systolic blood pressure, mmHg (n)	137±23 (178)	130±21 (112)	0.99 (0.98-1.00)	.30		
Diastolic blood pressure, mmHg (n)	71±13 (178)	67±14 (112)	1,01 (0,99-1,02)	.37		
Biochemical variables						
Hemoglobin- g/dl(n) ‡	11.0±2.1(155)	10.6±2.0 (100)	1,06 (0,94-1,19)	.38		
Hematocrit - % (n) ‡	32.5±6.3 (146)	31.4±5.8 (94)	0.97 (0.93-1.01)	.16		
White cell count > 20000 n/µliter - no. (%) (reference: <20000)‡	14/147 (9.5)	20/93 (21.5)	2.47 (1.19-5.11)	.02		

eTable 3. Bivariable and Multivariable Analysis of Factors Associated With the Primary Outcome (continued)

Recent surgical history, No. (%)				.38		
- Elective	96 (53.9)	56 (48.7)	1.23 (0.77-1.97)			
Emergency	82 (46.1)	59 (51.3)	reference			
Upper abdominal surgery, No. (%)	108/178 (60.7)	76/115 (66.1)	1.26 (0.78-2.06)	.35		
Type of surgery, No. (%)				.17		
Oesophagectomy	8/172 (4.7)	15/111 (13.5)	reference			
Gastrectomy	22/172 (12.8)	12/111 (10.8)	0.29 (0.09-0.88)			
Colorectal resection	44/172 (25.6)	24/111 (21.6)	0.29 (0.11-0.78)			
Liver resection	51/172 (29.7)	28/111 (25.2)	0.29 (0.11-0.78)			
Pancreatico-duodenectomy	15/172 (8.7)	9/111 (8.1)	0.32 (0.10-1.05)			
Other procedures	32/172 (18.6)	23/111 (20.7)	0.38 (0.14-1.05)			
Oesophagectomy vs every other types of surgery (reference: No)	8/172 (4.7)	15/111 (13.5)	3.19 (1.30-7.78)	.011	4.059 (1.559-10.5572)	.004
Laparotomysurgery (reference: No) – No. (%)	157/175 (89.7)	106/115 (92.2)	1.18 (0.50-2.78)	.70		
Vertical midline incision (reference: No)	97/152 (63.8)	72/106 (67.9)	1.20 (0.71-2.03)	.49		
Transverse incision (reference: No)	59/151 (39.1)	32/105 (30.5)	0.68 (0.40-1.16)	.16		
Other (reference: No)	5/154 (3.3)	6/105 (5.7)	1.54 (0.56-4.23)	.40		
Laparoscopic surgery (reference: No), No. (%)	21/175 (12.0)	11/115 (9.7)	0.78 (0.36-1.69)	.53		
Thoracotomy associated (reference: No), No. (%)	5/173 (2.9)	/114 (4.4)	1.54 (0.44-5.45)	.53		
Epidural analgesia (reference: No), No. (%)	21/178 (11.8)	23/115 (20.0)	1.87 (0.98-3.56)	.06		
Time of surgical procedure – hr	4.2±2.7 (175)	4.2±2.5 (112)	0,97 (0,88-1,06)	.44		
Extubated< 6-hr after the end of surgery, No. (%) (reference: >6 hr)	123/178 (69.1)	64/115 (55.7)	0.56 (0.34-0.91)	.02		
Acute Respiratory Failure specific risk factors						
Respiratory rate, breaths/min	28.3±7.5 (168)	28.9±7.5 (106)	0,99 (0,96-1,02)	.65		
Time from end of surgery to acute respiratory failure, days	2.4±1.7 (175)	2.6±1.6 (112)	0,96 (0,83-1,1)	.58		
Time from extubation to acute respiratory failure, days	2.0±1.7 (169)	1.8±1.4 (113)	1,04 (0,9-1,21)	.57		
Time from acute respiratory failure to inclusion in the study, hr	6.1±7.7 (178)	5.8±7.3 (115)	0.99 (0.96-1.02)	.68		
Causes of acute respiratory failure						
Atelectasis (reference: No)	113/176 (64.2)	74/114 (64.9)	1.03 (0.63-1.69)	.90		
Copious tracheal secretions (reference: No)	59/174 (33.9)	53/114 (46.5)	1.69 (1.04-2.75)	.03		
Pneumonia (reference: No)	37/173 (21.4)	26/111 (23.4)	1.12 (0.64-1.99)	.69		
Pulmonary edema (reference: No)	30/175 (17.1)	14/114 (12.3)	0.68 (0.34-1.34)	.26		
Pleural effusion (reference: No)	19/178 (10.7)	18/115 (15.7)	1.52 (0.51-5.41)	.79		
Pulmonary embolism (reference: No)	11/172 (6.4)	6/112 (5.4)	0.83 (0.30-2.31)	.72		

eTable 3. Bivariable and Multivariable Analysis of Factors Associated With the Primary Outcome (continued)

Arterial blood gas						
pH‡	7.43±0.07 (159)	7.40±0.08 (101)	0.01 (< 0.01-0.33)	.01		
PaO_2:FiO_2, mm Hg‡	202.3±67.1 (159)	182.2±73.3 (101)	0.99 (0.99-1.00)	.02		
$PaCO_2$, mm Hg‡	37.5±6.8 (159)	38.2±6.6 (101)	1.02 (0.98-1.06)	.27		
HCO_3^-, mmol/liter‡	24.5±3.7 (159)	24.0±4.1 (101)	0.97 (0.91-1.03)	.32		

Data are displayed as number of patients/Total (%) or mean±SD.
#Reference increment for each reported continuous variable is one point.
* Multivariable model adjusted for COPD, ischemic heart disease, Chronic heart failure and BMI>30. Variables included in the multivariable analysis where selected if the p value was <0.15 in the bivariable analysis. Hosmer and Lemeshow Goodness-of-Fit p=0.18.
** The Simplified Acute Physiology Score II is based on 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease. For the multivariable analysis, Simplified Acute Physiology Score II variable was dichotomized as upper and lower 40.
† The score on the Sequential Organ Failure Assessment (SOFA) includes subscores ranging from 0 to 4 for each of five components (circulation, lungs, liver, kidneys, and coagulation). Aggregated scores range from 0 to 20, with higher scores indicating more severe organ failure.
‡ Multiple imputation performed

eTable 4. Reasons for Re-intubation, as Defined in the Protocol Guidelines, According to Study Group

	Standard Oxygen Therapy (N = 66)	**Noninvasive Ventilation (N = 49)**	***P* Value**
No tolerance to noninvasive ventilation	N.A	2 (4.1)	N.A
Lack of improvement in respiratory distress (SOFA-respiratory >2)*	40 (60.6)	24 (49.0)	.21
Hemodynamic instability (SOFA-hemodynamic >2)*	1 (1.5)	3 (6.1)	.31
Neurologic disability (Glasgow score < 10)*	5 (7.6)	2 (4.1)	.69
Renal disability (SOFA-renal >2)*	0 (0)	0 (0)	.99
Cardiac arrest	2 (3.0)	1 (2.1)	.99
Return to operating room for new surgery procedure	16 (24.2)	16 (32.7)	.31
Others	2 (3.0)	1 (2.1)	.99

Data are displayed as number (%) of patients.
* Score on the Sequential Organ Failure Assessment (SOFA) ranging from 0 to 4 for each of components.
N.A: Not Applicable.

eTable 5. Primary and Secondary Outcomes According to Study Group

Variable	Standard Oxygen Therapy (N = 145)	Noninvasive Ventilation (N = 148)	Absolute rate difference with Noninvasive Ventilation (95% CI)	*P* Value
Outcome				
healthcare associated infections to Day 7, No. (%)	44 (30.3)	27 (18.2)	-11,93 (-20,94 to -2,93)	.016
Lung	32 (22.1)	15 (10.1)	-1,42 (-5,84 to 3)	.005
Urinary tract	5 (3.4)	3 (2.0)	0,68 (-1,33 to 2,68)	.49
Catheter	0 (0.0)	1 (0.7)	1,96 (-3,43 to 7,34)	1.00
Bacteremia	5 (3.4)	8 (5.4)	-1,49 (-7,68 to 4,69)	.47
Surgical-site infection	10 (6.9)	8 (5.4)	-11,93 (-20,94 to -2,93)	.60
healthcare associated infections to Day 14, No. (%)*	51 (38.1)	39 (27.6)	-10,4 (-22,18 to 1,38)	.07
Lung	33 (24.6)	19 (13.5)	-11,15 (-21,1 to -1,21)	.02
Urinary tract	8 (6.0)	7 (5.0)	-1,01 (-7,11 to 5,1)	.71
Catheter	1 (0.7)	1 (0.7)	-0,04 (-2,78 to 2,7)	.97
Bacteremia	10 (7.5)	8 (5.7)	-1,79 (-8,38 to 4,8)	.55
Surgical-site infection	14 (10.5)	13 (9.2)	-1,23 (-9 to 6,54)	.73
healthcare associated infections to Day 30, No. (%)**	63 (49.2)	43 (31.4)	-17,83 (-30,22 to -5,44)	.003
Lung	38 (29.7)	20 (14.6)	-15,09 (-25,72 to -4,45)	.003
Urinary tract	13 (10.2)	8 (5.8)	-4,32 (-11,61 to 2,98)	.19
Catheter	1 (0.8)	2 (1.5)	0,68 (-2,6 to 3,96)	.99
Bacteremia	16 (12.5)	11 (8.0)	-4,47 (-12,54 to 3,6)	.23
Surgical-site infection	20 (15.6)	18 (13.1)	-2,49 (-11,7 to 6,73)	.56

*Missing data for healthcare associated infections at D14 in Standard Oxygen Therapy n=11 and NIV n=7.
**Missing data for healthcare associated infections at D30 in Standard Oxygen Therapy n=17 and NIV n=11.

eTable 6. Clinical Pulmonary Infection Score (CPIS) and Microorganisms Causing Pneumonia According to Study Group

	Standard Oxygen Therapy (N = 38)	**Noninvasive Ventilation (N = 20)**
Intubated at the time of the diagnosis– No. (%)	30 (78.9)	14 (70.0)
Time from inclusion to pneumonia diagnosis (d)	11.8±9.8	13.9±8.3
Clinical pulmonary infection score, mean±SD	8.0±1.7	8.5±1.5
Temperature points	0.9±0.8	0.9±0.9
Leukocyte points	1.3±0.6	1.0±0.6
Tracheal secretions	1.3±0.9	1.4±0.9
Oxygenation	1.5±0.9	1.5±0.9
Radiography	1.3±0.6	1.5±0.7
Culture of pulmonary samples	1.8±0.7	2.0±0.0
Type of respiratory tract samples, No. (%)		
Bronchoalveolar lavage	16 (42.1)	6 (30)
Blinded protected telescoping catheter	10 (26.3)	5 (25)
Tracheal sample	9 (23.7)	5 (25)
None	3 (7.9)	4 (20)
Polymicrobial pneumonia, No. (%)	19 (50)	10 (50)
Microorganisms, No	**58**	**33**
- Gram-negative bacilli, No. (%)	37 (63.8)	22 (66.6)
Enterobacteriaceae	21 (36.2)	7 (21.2)
Pseudomonas aeruginosa	5 (8.6)	6 (18.2)
Klebsiella pneumoniae	5 (8.6)	5 (15.2)
Stenotrophomonas maltophilia	2 (3.5)	2 (6.1)
Haemophilus sp.	3 (5.2)	2 (6.1)
Acinetobacter sp.	1 (1.7)	0 (0)
- Gram-positive cocci, No. (%)	14 (24.1)	9 (27.2)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	4 (6.9)	3 (9.1)
Methicillin- resistant *Staphylococcus* (MRSA)	1 (1.7)	1 (3.0)
Streptococcus pneumoniae	5 (8.6)	3 (9.1)
Enterococcus sp.	4 (6.9)	2 (6.1)
***Candida* sp., No. (%)**	7 (12.1)	2 (6.1)

Values are displayed as number (%) or mean±SD.
The Clinical Pulmonary Infection Score (CPIS) was calculated from the first five variables (see table CPIS). The CPIS gram/culture was calculated from the CPIS score by adding two more points when gram stains or culture were positive. A score of more than six at baseline or after incorporating the gram stains (CPIS gram) or culture (CPIS culture) results was considered suggestive of pneumonia.
Pneumonia can have been caused by more than one species of gram-negative or gram-positive microorganisms and/or of *Candida*.

Trial protocol - NIVAS Study

METHODS

Study oversight

The Non-Invasive Ventilation after Abdominal Surgery (NIVAS) was an investigator-initiated, multi-center, stratified, two-arm parallel-group trial with a computer-generated allocation sequence and an electronic system-based randomization. The study protocol and statistical analysis plan were approved for all centers by a central Ethics Committee (Comité de Protection des Personnes Sud Mediterranée III, Nimes, France) according to French law. The NIVAS study was conducted in accordance with the declaration of Helsinki and was registered at http://www.clinicaltrials.gov with trial identification number NCT01971892. Depending on the severity of the illness and competency, informed written or witnessed oral consent from the patient, or witnessed consent from a relative, was obtained upon study inclusion. Whenever possible, written consent for continued participation in the trial was obtained from the patient in the subsequent 7 days.

An independent data and safety monitoring committee oversaw the study conduct and reviewed blinded safety data, with interim analyses performed after the inclusion of 100 and 200 patients. The steering committee vouched for the accuracy and completeness of the data and analysis, and the fidelity of the study to the protocol, and took the decision to submit the manuscript for publication. The writing committee wrote all drafts of the manuscript without editorial assistance; all the authors provided revisions and comments. There was no industry support or involvement in the trial. Patients were screened and underwent randomization between May 2013 and September 2014 at 20 ICUs in 17 French university and 3 non-university hospitals. All sites had a long experience with NIV (more than 10 years of NIV use for ARF, and more than 5 years of NIV use for ARF following abdominal surgery). Randomization was performed centrally, with the use of a computer-generated and blinded assignment sequence. Randomization was stratified according to study site, age (less or more than 60 years), site of surgery (upper or lower abdominal) and according to the use of postoperative epidural analgesia, which may influence outcomes. Treatment assignments were concealed from research staff, the statistician and the data monitoring/safety committee.

Patients

Inclusion criteria

1. Adult patients older than 18 years
2. Laparoscopic or non-laparoscopic elective or non-elective abdominal surgery under general anesthesia
3. Acute respiratory failure occurring within 7 days of the surgical procedure, defined as presence and persistence > 30 minutes of at least one of the two following:

   1) a respiratory rate above 30 breaths/min and

   2) clinical signs suggesting respiratory muscle fatigue, labored breathing, or both, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retractions and

   3) hypoxemia defined by a partial oxygen pressure lower than 60 mmHg when breathing room air, or lower than 80 mmHg with 15 liters per minute of oxygen or a peripheral oxygen saturation of ≤90% breathing room air (PaO_2/FIO_2≤300 mmHg).
4. And informed consent obtained
5. And valid affiliation to the Social Security System

Exclusion criteria

1. Limitation of therapy
2. Contraindications to noninvasive ventilation: required immediate tracheal intubation and invasive mechanical ventilation, hemodynamic instability defined by systolic arterial blood pressure below 90 mm Hg or mean arterial blood pressure below 65 mm Hg, use of vasopressors; a Glasgow Coma Scale score of 12 points or less (on a scale from 3 to 15, with lower scores indicating reduced levels of consciousness)
3. Required an emergent surgical procedure (operation that had to be performed within 12 hours after inclusion in the study)
4. Previous recruitment in another trial.
5. Pregnancy
6. Refusal to participate

Interventions and trial settings for NIVAS trial

Patients were randomly assigned to receive either NIV (NIV-group) or standard-oxygen therapy alone (oxygen-group) from randomization until day 30 or ICU discharge, whichever came first. Patients assigned to standard-oxygen therapy received supplemental oxygen at a rate of up to 15 liters per minute in order to maintain peripheral oxygen saturation ≥94%. In the intervention group (NIV-group), NIV was delivered through a face mask connected to an ICU or NIV-dedicated ventilator, using either heated humidifier or heat and moisture exchanger to warm and humidify inspired gases. NIV was started at an inspiratory positive airway pressure of 5 cm of water and was increased to a maximum inspiratory pressure of 15 cm of water aiming to achieve an expiratory tidal volume between 6 to 8 ml per kilogram of predicted body weight and a respiratory rate of less than 25 breaths per minute. Positive-end expiratory airway pressure (PEEP) was started at 5 cm of water and was increased to a maximum of 10 cm of water. PEEP and inspired oxygen fraction were titrated to maintain an arterial oxygen saturation ≥94%. Ventilator settings were subsequently adjusted as needed for patient comfort. Patients in this group were encouraged to use NIV for at least 6 hours, continuously or fractioned, during the first 24 hours after randomization. Between NIV sessions, patients received standard-oxygen therapy as described above. The use of high-flow oxygen nasal cannulae (>15 liters per minute) was not permitted in either group. The decision regarding when to discontinue NIV was left to the attending physician. Participants who did not receive the assigned treatment or who did not adhere to the protocol were followed up in full, and their data were included in the analysis according to the intention-to-treat principle (see statistical analysis section). All other aspects of patient care in both groups were conducted according to each center's routine clinical practice.

Criteria of endotracheal intubation

To reduce the risk of delayed re-intubation and to ensure the consistency of indications for re-intubation between all trial sites, predefined criteria were applied in all participating centers. In the two groups, immediate re-intubation was performed if the patients met any of the following predefined major clinical events: respiratory or cardiac arrest; respiratory pauses with loss of consciousness or gasping for air; massive aspiration; persistent inability to clear respiratory secretions; heart rate below 50 beats per min with loss of alertness; and severe hemodynamic instability without response to fluids and vasoactive drugs. After re-intubation,

all patients were ventilated with the same ventilation protocol, according to the low-tidal-volume protective ventilatory strategy.

Data collection and definitions

Causes of acute respiratory failure (ARF)

We assigned causes of ARF following extubation, with adapted published definitions: upper-airway obstruction; aspiration or excess respiratory secretions; severe encephalopathy; congestive heart failure; pneumonia and atelectasis. Severe encephalopathy was defined by Glasgow coma scale of 12 points or less (on a scale from 3 to 15, with lower scores indicating reduced levels of consciousness).

Atelectasis was defined as lung opacification with shift of the mediastinum, hilum or hemi-diaphragm towards the affected area and compensatory overinflation in the adjacent non-atelectatic lung.

Health-Care associated infections

Diagnostic criteria for health-care associated infections were adapted from CDC criteria. The sites and dates of diagnosis of all healthcare associated infections were recorded as well as antibiotic regimens given during the ICU stay within 30 days after inclusion in the study.

Pneumonia, urinary tract infection, central venous catheter-related infection, bacteremia and surgical-site infection, occurring both at least 48 hours after ICU admission and after inclusion in the study were collected according to the following definitions.

Pneumonia was suspected in patients with a combination of new and persistent lung infiltrates on chest X-ray, a temperature greater than 38°C, and macroscopically purulent tracheal secretions while receiving either standard oxygen therapy, noninvasive ventilation or invasive mechanical ventilation. Pneumonia was ascertained by the positivity of a quantitative respiratory culture, defined as at least 1 microorganism recovered at concentration of at least 1000 colony forming units per mL for blinded protected telescoping catheter, of at least 10000 colony forming units per mL for broncho-alveolar lavage and of at least 1000000 colony forming units per mL for tracheal aspirates. In patients clinically suspected of having pneumonia but treated with noninvasive ventilation, the positivity of a blinded protected telescoping catheter culture at the same significant threshold, when available, or the sole administration of new antibiotics in the absence of other sites of infection was used to characterize the presence of pneumonia.

The modified Clinical Pulmonary Infection Score (CPIS) at suspected pneumonia was

calculated from the first five variables (see table CPIS). The CPIS gram/culture was calculated from the CPIS score by adding two more points when gram stains or culture were positive. A score of more than six at baseline or after incorporating the gram stains（CPIS gram）or culture（CPIS culture）results was considered suggestive of pneumonia.

The Modified Clinical Pulmonary Infection Score（modified CPIS）

CPIS Points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant＋purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature, ℃	≧36.5 and≦38.4	≧38.5. and≦38.9	≧39 or≦36.4
Leukocytes count, per mm^3	≧4,000 and≦11,000	＜4,000 or＞ 11,000	＜4,000 or＞11,000 ＋ band forms≧500
P_{aO2}/F_{IO2}, mmHg	＞240 or ARDS		≦240 and no evidence of ARDS
Microbiology	Negative		Positive

Urinary tract infection was defined by the association of fever (body temperature greater than 38°C) and a urine culture with no more than two species of organisms, at least one of which is a bacteria of at least 100000 colony forming units per ml, in patients with no other evident source of infection.

Catheter-related infection was defined as a combination of fever (body temperature greater than 38°C), a quantitative catheter-tip culture eluate in broth showing at least one microorganism in a concentration of at least 1000 colony forming units per mL, and resolution of fever within 48 h after catheter removal and without any change in antimicrobial therapy, and no other evident source of infection identified.

Primary bacteremia was defined as a combination of fever (body temperature greater than 38°C), at least 1 positive blood culture (two or more blood cultures drawn on separate occasions when coagulase-negative staphylococci were isolated) not related to an infection at another site.

Surgical-site infection diagnostic was performed according standard CDC definitions (Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999: Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250-78.).

An independent infectious disease specialist reviewed all clinical and microbiological informations for each patient.

TABLE 1
CRITERIA FOR DEFINING A SURGICAL SITE INFECTION (SSI)*

Superficial Incisional SSI

Infection occurs within 30 days after the operation
and
infection involves only skin or subcutaneous tissue of the incision
and at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.[33]

Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
and
infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision
and at least *one* of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopatholog ic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/Space SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation
and
infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation
and at least *one* of the following:

1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

* Horan TC et al.[32]
† National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.
‡ If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.

Definitions for outcomes

The primary outcome for comparing NIV and standard-oxygen therapy was any cause of re-intubation within 7 days following randomization. Causes and time to re-intubation were recorded. Secondary outcomes included gas exchange, healthcare associated infections rate within 30 days, the number of ventilator-free days (i.e. days alive and without invasive mechanical ventilation) between day-1 and day-30, antibiotic use duration and numbers, ICU and in-hospital lengths of stay, 30 and 90-day mortality.

Statistical Analysis Plan

(NIVAS Study)

Population

We will perform all the analyses of the trial on the intention-to-treat population. The intention-to-treat population is defined by all randomised patients except patients who would be randomized despite being not eligible for randomisation according to inclusion/exclusion criteria. A modified intention-to-treat analysis will be done on the primary outcome including patients who will not return to operating room for reintervention (i.e, patients in whom trachea will be intubated for return to operating room will not be included in this modified intention-to-treat analysis). Patients who will return to operating room for another surgical procedure and will systematically re-intubated will be considered as a treatment failure (reach primary outcome in intention-to-treat analysis).

Sample size

We estimate that with a sample of 150 patients per group who could be evaluated for the primary efficacy outcome, the study will have at least 90% power to determine both the superiority for the intention-to-treat analysis and for the modified intention-to-treat analysis (excluding the patients that will return to the operating room for reintervention) of non invasive ventilation (NIV-group) as compared with standard-oxygen therapy (oxygen-group). For the intention-to-treat analysis, the following assumptions are made: a 65% event rate in the oxygen-group and a 40% event rate in the NIV-group (absolute risk reduction with NIV of at least 25%). Further assumptions (15% of the included patients) are made relating to patients randomized despite being not eligible for randomisation according to inclusion/exclusion criteria and loss to follow-up for the primary endpoint. For the modified intention-to-treat analysis, the same assumptions are made, with an estimated rate of patients who will return to operating room for reintervention after intubation to be as high as 33% .

Interim analyses

Two interim analysis will be planned for early stopping of the study owing to safety (mortality within 90 days) after the first 100 and 200 patients included with the use of a prespecified Haybittle–Peto efficacy boundary (α = 0.001 for the two interim analysis). These interim analysis will be performed by an independent data monitoring and safety committee. If an analysis of the interim data from 100 or 200 patients fulfils the Haybittle-Peto criterion the inclusion of further patients will be paused and an analysis including patients randomized during the analysis period will be performed. If this second analysis also fulfils the Haybittle-Peto criterion the independent data monitoring and safety committee will recommend stopping the trial. The independent safety monitoring committee included the following physicians: Pr Karim Asehnoune, Pr Xavier Capdevila and Pr Pierre Michelet.

Analyses

Primary analysis:

Unadjusted Chi-square test (or Fisher's exact test as appropriate) for binary outcome measures. Unpaired t-test (or Wilcoxon signed-rank testing as appropriate) for continuous outcome measures. Relative risks will be presented for binary variables and mean differences for continuous variables with 95% confidence interval.

Secondary analysis:

Multiple (logistic) regression for the primary outcome with the following covariates (variables will be selected if P value is less than 0.15 in the univariate analysis and a stepwise procedure will be used to select the final model. Interactions between variables will be tested):

- Patient-specific risk factors
  - Age
  - Age ≥ 60 years old

- Male gender
- Body mass index
- Body mass index ≥ 30 kg/m²
- Simplified Acute Physiology Score II at entry into the study
- Simplified Acute Physiology Score II at entry into the study > 40
- Sequential Organ Failure Assessment score at entry into the study
- Preexisting conditions : current smoker, alcohol intake, psychotropic use, chronic arterial hypertension, ischemic heart disease, chronic heart failure, chronic obstructive pulmonary disease, liver cirrhosis, cancer, sepsis
- Clinical variables : body temperature, heart rate, systolic blood pressure, diastolic blood pressure
- Biochemical variables : hemoglobin, hematocrit, white cell count, white cell count > 20000 n/µliter

• Surgery characteristics-specific risk factors

- Recent surgical history : elective, emergency
- Upper abdominal surgery
- Type of surgery : oesophagectomy, gastrectomy, colorectal resection, liver resection, pancreatico-duodenectomy, other procedures
- Oesophagectomy vs all other types of surgery
- Laparotomy surgery : vertical midline incision, transverse incision, other
- Laparoscopic surgery
- Thoracotomy associated surgery
- Epidural analgesia
- Time of surgical procedure

• Acute respiratory failure-specific risk factors

- Respiratory rate
- Time from end of surgery to acute respiratory failure
- Time from extubation to acute respiratory failure

- Time from acute respiratory failure to inclusion in the study
- Causes of acute respiratory failure (atelectasis, copious tracheal secretions, pneumonia, pulmonary edema, pleural effusion, pulmonary embolism, others)
- Arterial blood gases : pH, PaO2/FiO2, PaCO2, $HCO3^-$

We will compare the primary outcome in prespecified subgroups defined by stratification criteria according to age (less or more 60 years), site of surgery (upper or lower abdominal) and use or not use of epidural analgesia.

The Kaplan-Meier curves for 30-days re-intubation and for 90-days mortality will be plotted and compared by the log-rank test.

Outcomes

Primary outcome measure:

- Re-intubation within 7 days following randomization.

Secondary outcome measures:

- Reintubation within 14 days
- Reintubation within 30 days
- ICU-acquired infection within 7, 14 and 30 days
- Mortality within 30 days and 90-days
- Duration of Invasive Ventilation within 14 days, 30 days,90 days
- Invasive ventilatory free days within 14 days, 30 days, 90 days
- Intensive care unit (ICU) and in hospital lengths of stay within 90 days
- ICU free days within 14 days, 30 days, 90 days

Tolerance of NIV will also be analyzed separately:

- leaks around the mask
- dry mouth and/or nasal congestion

- copious bronchial secretions
- ocular irritation
- skin ulcerations
- gastric distension
- anxiety
- bronchial secretions (no/moderate/excessive)

NIV settings and monitored parameters will be presented for reintubated and for non reintubated patients in the noninvasive ventilation group.

Missing data

Due to the low rate of predicted missing values, we will not use any imputation method. Analyses will be performed on the complete cases. We expect to have full data sets on all patients. If not, we will indicate in each table the number of observed data. In case of unexpected high rate of missing values (>15%), we will use for the secondary outcomes a multiple imputation method.

Software

All data analysis will be conducted with SAS statistical software, version 9.3.