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Effect of Intraoperative High Positive End-Expiratory Pressure (PEEP) With Recruitment Maneuvers vs Low PEEP on Postoperative Pulmonary Complications in Obese Patients
A Randomized Clinical Trial

Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVEnet) for the Clinical Trial Network of the European Society of Anaesthesiology

IMPORTANCE An intraoperative higher level of positive end-expiratory positive pressure (PEEP) with alveolar recruitment maneuvers improves respiratory function in obese patients undergoing surgery, but the effect on clinical outcomes is uncertain.

OBJECTIVE To determine whether a higher level of PEEP with alveolar recruitment maneuvers decreases postoperative pulmonary complications in obese patients undergoing surgery compared with a lower level of PEEP.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial of 2013 adults with body mass indices of 35 or greater and substantial risk for postoperative pulmonary complications who were undergoing noncardiac, nonneurological surgery under general anesthesia. The trial was conducted at 77 sites in 23 countries from July 2014-February 2018; final follow-up: May 2018.

INTERVENTIONS Patients were randomized to the high level of PEEP group (n = 989), consisting of a PEEP level of 12 cm H_2O with alveolar recruitment maneuvers (a stepwise increase of tidal volume and eventually PEEP) or to the low level of PEEP group (n = 987), consisting of a PEEP level of 4 cm H_2O. All patients received volume-controlled ventilation with a tidal volume of 7 mL/kg of predicted body weight.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of pulmonary complications within the first 5 postoperative days, including respiratory failure, acute respiratory distress syndrome, bronchospasm, new pulmonary infiltrates, pulmonary infection, aspiration pneumonitis, pleural effusion, atelectasis, cardiopulmonary edema, and pneumothorax. Among the 9 prespecified secondary outcomes, 3 were intraoperative complications, including hypoxemia (oxygen desaturation with Spo_2 ≤92% for >1 minute).

RESULTS Among 2013 adults who were randomized, 1976 (98.2%) completed the trial (mean age, 48.8 years; 1381 [69.9%] women; 1778 [90.1%] underwent abdominal operations). In the intention-to-treat analysis, the primary outcome occurred in 211 of 989 patients (21.3%) in the high level of PEEP group compared with 233 of 987 patients (23.6%) in the low level of PEEP group (difference, −2.3% [95% CI, −5.9% to 1.4%]; risk ratio, 0.93 [95% CI, 0.83 to 1.04]; *P* = .23). Among the 9 prespecified secondary outcomes, 6 were not significantly different between the high and low level of PEEP groups, and 3 were significantly different, including fewer patients with hypoxemia (5.0% in the high level of PEEP group vs 13.6% in the low level of PEEP group; difference, −8.6% [95% CI, −11.1% to 6.1%]; *P* < .001).

CONCLUSIONS AND RELEVANCE Among obese patients undergoing surgery under general anesthesia, an intraoperative mechanical ventilation strategy with a higher level of PEEP and alveolar recruitment maneuvers, compared with a strategy with a lower level of PEEP, did not reduce postoperative pulmonary complications.

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Up to 18% of obese patients undergoing surgery have postoperative pulmonary complications,[1] which is almost twice the risk among normal weight or overweight patients.[2,3] Postoperative pulmonary complications prolong hospitalization and increase mortality.[3,4] In 2012, it was estimated that more than 310 million surgical procedures were conducted worldwide.[5] Given that the global prevalence of obesity is increasing,[6,7] the burden of postoperative pulmonary complications will increase if the number of surgical procedures remains unchanged over the coming decades.

Protective intraoperative mechanical ventilation has been associated with reduced incidence of postoperative pulmonary complications.[8,9] Among normal weight and overweight patients, low tidal volumes and low levels of positive end-expiratory pressure (PEEP) with alveolar recruitment maneuvers reduced the risk of major pulmonary and extrapulmonary complications compared with high tidal volumes and no PEEP.[10] However, when low tidal volumes were used in different ventilator strategies, a higher level of PEEP with alveolar recruitment maneuvers did not reduce the incidence of postoperative pulmonary complications compared with a lower level of PEEP.[11,12]

Obesity is associated with increased risk of atelectasis and impaired respiratory function during general anesthesia.[13] An approach using an intraoperative high level of PEEP and alveolar recruitment maneuvers prevented those alterations,[14,15] and has been proposed for routine intraoperative mechanical ventilation in obese patients.[13,16] Whether this approach improves postoperative outcomes remains uncertain.

The Protective Intraoperative Ventilation With Higher Versus Lower Levels of Positive End-Expiratory Pressure in Obese Patients (PROBESE) trial was conducted to test whether an intraoperative mechanical ventilation strategy with a higher level of PEEP and alveolar recruitment maneuvers reduces the incidence of postoperative pulmonary complications during the initial 5 postoperative days compared with a lower level of PEEP without alveolar recruitment maneuvers in obese patients undergoing surgery who are at increased risk for these complications.

Key Points

Question Does a high level of positive end-expiratory pressure (PEEP) with alveolar recruitment maneuvers decrease postoperative pulmonary complications in obese patients undergoing surgery compared with a low level of PEEP?

Findings In this randomized trial of 1976 obese adults undergoing noncardiac, nonneurological surgery under general anesthesia, the rate of pulmonary complications was 21.3% among those randomized to a strategy of mechanical ventilation combining alveolar recruitment maneuvers and a higher level of PEEP compared with 23.6% among those randomized to a strategy with a lower level of PEEP without alveolar recruitment maneuvers; however, the difference was not statistically significant.

Meaning An intraoperative mechanical ventilation strategy with a higher level of PEEP and alveolar recruitment maneuvers did not reduce postoperative pulmonary complications in obese patients.

Methods

Study Design and Oversight

This was an international, investigator-initiated, assessor-blinded randomized clinical trial. The protocol was published[17] and appears in Supplement 1. Amendments and changes to the trial protocol appear in Supplement 2. The final statistical analysis plan that was written prior to locking the database appears in Supplement 3. The institutional review board at each site approved the protocol. Written informed consent was obtained from all participating patients. A data and safety monitoring committee oversaw the conduct of the study and reviewed blinded safety data. Onsite monitoring for adherence to the trial protocol and completeness of data was conducted at the sites that included more than 60 patients.

Patients

Patients were included if they had a body mass index (calculated as weight in kilograms divided by height in meters squared) of 35 or greater, were scheduled for a laparoscopic or nonlaparoscopic surgery that was expected to exceed 2 hours under general anesthesia, and had an intermediate to high risk of developing postoperative pulmonary complications as indicated by an Assess Respiratory Risk in Surgical Patients in Catalonia score[18] of 26 or greater (eTable 1 in Supplement 4).

Patients were excluded if they were younger than 18 years, previously had lung surgery, had received invasive mechanical ventilation for longer than 30 minutes within the last 30 days prior to surgery, or had received chemotherapy or radiotherapy within 2 months prior to surgery. Additional exclusion criteria included cardiac and neurological surgery, intraoperative one-lung ventilation, planned reintubation after surgery, need for intraoperative prone or lateral decubitus positioning during surgery, or current participation in another interventional study.

In addition, patients were excluded if pregnant or had persistent hemodynamic instability or intractable shock, severe chronic obstructive pulmonary disease, severe cardiac disease, concurrent acute respiratory distress syndrome expected to require prolonged postoperative mechanical ventilation, severe pulmonary hypertension, intracranial injury or tumor, or neuromuscular disease (eMethods in Supplement 4).

Randomization and Interventions

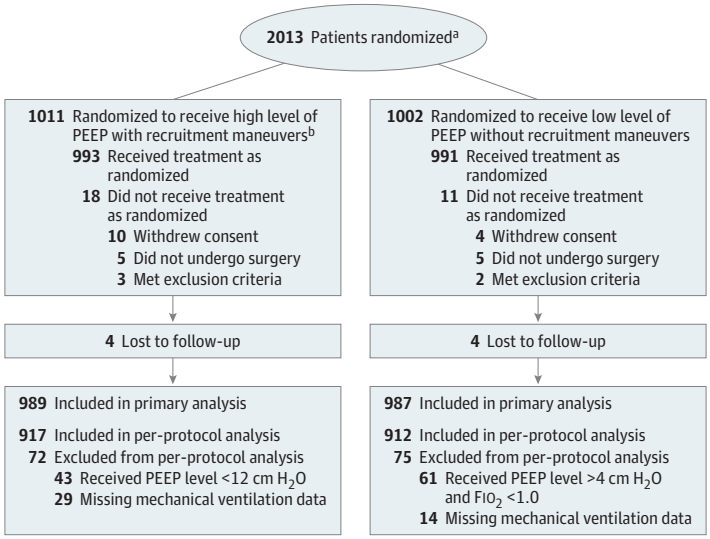
Randomization was based on a computer-generated allocation sequence and was performed using a password-protected, encrypted web interface. The 1:1 allocation sequence used permuted, random block sizes of 4, 6, and 8 and was stratified by study site.

Patients received volume-controlled mechanical ventilation with a tidal volume of 7 mL/kg of predicted body weight

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Figure 1. Flow Diagram of Patients Through Trial



For patients who met exclusion criteria, 2 were due to switching the patient during surgery to the lateral decubitus position and 3 were due to the patient having a body mass index lower than 35 on the day of surgery. F_{IO_2} indicates fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

[a] The number of patients assessed for eligibility is not reported because it was not collected at all sites.

[b] Recruitment maneuvers are an increase in airway pressure through a stepwise increase of tidal volume and eventually PEEP.

and were assigned to either (1) a PEEP level of 12 cm H_2O with alveolar recruitment maneuvers performed after endotracheal intubation, which were repeated every hour after any disconnection from the mechanical ventilator and before the end of surgery (high level of PEEP group) or (2) a PEEP level of 4 cm H_2O (low level of PEEP group) (**Figure 1**).

Alveolar recruitment maneuvers were standardized[17] and consisted of a stepwise increase of tidal volume and, if necessary, PEEP level was increased until an airway plateau pressure between 40 and 50 cm H_2O was achieved (eMethods in Supplement 4). All patients received the lowest fraction of inspired oxygen (F_{IO_2}), but not less than 0.4, that maintained greater than 92% peripheral oxygen saturation as measured by pulse oximetry (S_{PO_2}).

Tidal volume was set based on predicted body weight, which was calculated using standard formulas.[19] When S_{PO_2} decreased to 92% or lower, the general strategy was to increase F_{IO_2} in the low level of PEEP group and to increase PEEP in the high level of PEEP group (eTable 2 in Supplement 4).

Other aspects of perioperative care were managed according to each study site's routine practice; however, optional recommendations also were provided (eMethods in Supplement 4).

Blinding

The investigators who were responsible for assessing the primary outcomes were blinded to study group assignment. However, the attending anesthesiologists, intraoperative nursing staff, and intraoperative assessors were not blinded to study group assignment.

Primary Outcome

The primary outcome was a composite of postoperative pulmonary complications and was defined as having occurred if any preselected complication developed within the first 5 postoperative days. The preselected complications included mild, moderate, and severe respiratory failure; acute respiratory distress syndrome; bronchospasm; new pulmonary infiltrates; pulmonary infection; aspiration pneumonitis; pleural effusion; atelectasis; cardiopulmonary edema; and pneumothorax.

Secondary Outcomes

The 9 secondary outcomes included (1) the composite of severe postoperative pulmonary complications, (2) postoperative extrapulmonary complications (systemic inflammatory response, sepsis, severe sepsis, septic shock, extrapulmonary infection, coma, acute myocardial infarction, acute kidney failure, disseminated intravascular coagulation, gastrointestinal failure, and hepatic failure), (3) impaired postoperative wound healing, (4) the unexpected need for intensive care unit admission or readmission, (5) the number of hospital-free days at postoperative day 90, the intraoperative adverse events of (6) hypoxemia (defined as oxygen desaturation with S_{PO_2} ≤92% for >1 minute), (7) hypotension (defined as systolic arterial pressure <90 mm Hg for >2 minutes), and (8) bradycardia (defined as heart rate <50 beats/min or a decrease >20% if the heart rate was <50 beats/min before a recruitment maneuver), and (9) in-hospital mortality.

Post Hoc Outcomes

Post hoc outcomes included 5-day mortality, the need for rescue due to desaturation, and the need for vasoactive drugs.

Statistical Analysis

Anticipating a rate of postoperative pulmonary complications of 40% in the low level of PEEP group[18,20] and assuming a dropout rate of 5%, it was originally determined that an enrollment of 748 patients would provide 80% power to detect a relative risk of 0.75 for the incidence of postoperative pulmonary complications at a 2-sided α level of .05.

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Among normal weight and overweight patients undergoing abdominal surgery, an intraoperative protective mechanical ventilation strategy consisting of low tidal volume and low level of PEEP with alveolar recruitment maneuvers was associated with a relative risk of postoperative pulmonary complications between 0.19 and 0.69 compared with a nonprotective strategy.[14] Because the present study focused on the effects of PEEP with alveolar recruitment maneuvers and because tidal volume was protective in both groups, a more conservative relative risk of 0.75 was considered to be appropriate by the steering committee while still being clinically relevant.

After blinded data review of 618 patients by the data and safety monitoring committee, the pooled incidence of postoperative pulmonary complications was approximately 20%. Sample size could be recalculated without affecting the type I error rate.[21] Therefore, it was conservatively assumed that the rate of postoperative pulmonary complications would be 20% in the low level of PEEP group. Accordingly, 2013 patients would provide 80% power to detect a relative risk of 0.75 for the primary end point at a 2-sided α level of .05, assuming a dropout rate of 5%, and interim analyses for efficacy, harm, and futility at 50%, 75%, and 100% of the total number of patients for which a nonbinding sequential design with stopping rules was used (eFigure 1 in Supplement 4). The data and safety monitoring committee recommended continuation of the trial on the basis of these analyses.

Patients were analyzed on an intention-to-treat basis according to their randomization group. The analysis data set included all patients who were randomized and had general anesthesia for eligible surgery. Because there were no missing data for the primary outcome, only complete case analysis was performed. All patients were followed up for the duration of the trial unless they withdrew consent. In such cases, data were censored at the time that consent was withdrawn. Additional analyses were performed in the per-protocol population that excluded patients with missing mechanical ventilation data and either receiving (1) a PEEP level greater than 4 cm H_2O and who had an FIO_2 of less than 1.0 in the low level of PEEP group or (2) a PEEP level of less than 12 cm H_2O in the high level of PEEP group.

The effect of the intervention on the primary outcome is reported as number and percentage and estimated with risk ratios (RRs) and 95% CIs that were calculated using the Wald likelihood ratio approximation test and the χ^2 test for hypothesis testing. The 2-sided α level for the primary outcome was .044 to account for the interim analyses. Time until postoperative pulmonary complications was assessed using Kaplan-Meier survival curves, and reported as hazard ratios and 95% CIs estimated from a Cox proportional hazards model. The Schoenfeld residuals against the transformed time was used to test the proportional hazards assumptions. As a sensitivity analysis, the effect of the intervention on the primary outcome was reestimated using a generalized linear mixed-effects model with a stratification variable (study site) as the random effect. Because the primary outcome was a composite outcome, sensitivity analyses also were performed.

For other binary outcomes, the effect of the intervention was assessed with RRs and 95% CIs that were calculated using the Wald likelihood ratio approximation test and the χ^2 test for hypothesis testing. The effect of the intervention on hospital-free days at day 90 was estimated using the *t* test and reported as the mean difference between groups. The effect of the intervention on 5-day mortality was estimated using Kaplan-Meier curves, and the hazard ratios and 95% CIs were calculated using Cox proportional hazards models without adjustment for covariates. The Schoenfeld residuals against the transformed time were used to test the proportional hazards assumptions. For the secondary outcomes, a significance level of .05 was used without adjusting for multiple comparisons. Because of the potential for type I error due to multiple comparisons, the findings from the analyses of the secondary end points should be interpreted as exploratory.

The treatment effects were analyzed according to the following prespecified subgroups: (1) nonlaparoscopic vs laparoscopic surgery; (2) body mass index less than 40 vs 40 or greater; (3) baseline SpO_2 of less than 96% vs 96% or greater; (4) peripheral vs upper abdominal procedures; and (5) waist-to-hip ratio less than 1.0 vs 1.0 or greater. The analyses for the heterogeneity of effects across subgroups used treatment × subgroup interaction terms added to a generalized linear model considering a binomial distribution.

Complete case analysis was performed for all outcomes. Post hoc analyses comparing the number of procedures for rescue due to hypoxemia, and the need for vasoactive drugs in both groups were performed.

Baseline characteristics were reported as counts and percentages, means and standard deviations, or medians and interquartile ranges whenever appropriate. Hypothesis tests were 2-sided at an α level of .05. All analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing).

Results

From July 2014 through February 2018, a total of 2013 adults were randomized (mean age, 48.8 years; 1381 [69.9%] women; 1778 [90.1%] underwent abdominal operations) at 77 sites in 23 countries (a list of the sites appears in Supplement 4). Twenty-nine patients were excluded after randomization, resulting in 1984 patients who met the criteria for the intention-to-treat analysis. Another 8 patients were lost to follow-up after surgery (4 patients in each treatment group). Final follow-up occurred during May 2018.

Therefore, data from 1976 patients were included in the intention-to-treat analysis. Data from 1829 patients were included in the per-protocol analysis. Baseline characteristics of the 2 groups appear in **Table 1**.

Intraoperative Procedures

Intraoperative variables appear in **Table 2** and in eTables 3-6 in Supplement 4. Tidal volumes were comparable between groups (eFigure 2 in Supplement 4). The mean level of PEEP was 12.0 cm H_2O (SD, 1.1 cm H_2O) in the high level of PEEP group

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Table 1. Baseline Patient Demographic and Perioperative Characteristics

Characteristic	High Level of PEEP (n = 989)[a]	Low Level of PEEP (n = 987)[a]
Age, mean (SD), y	48.6 (13.8)	48.9 (13.3)
Sex, No. (%)		
Male	295 (29.8)	300 (30.4)
Female	694 (70.2)	687 (69.6)
Height, mean (SD), cm	166.1 (9.7)	166.2 (9.6)
Weight, mean (SD), kg	121.8 (24.8)	120.1 (24.1)
Body mass index, mean (SD)[b]	44.0 (7.4)	43.5 (7.1)
35-40, No. (%)	337 (34.1)	378 (38.3)
>40, No. (%)	652 (65.9)	609 (61.7)
Waist-to-hip ratio, mean (SD)	1.01 (0.21)	1.00 (0.18)
<1.0, No./total No. (%)	467/914 (51.1)	457/906 (50.4)
≥1.0, No./total No. (%)	447/914 (48.9)	449/906 (49.6)
ARISCAT score, mean (SD)[c]	37.2 (7.6)	37.2 (7.1)
Intermediate risk, No. (%)	831 (84.0)	830 (84.1)
High risk, No. (%)	158 (16.0)	157 (15.9)
Preoperative Risk Factors for Postoperative Pulmonary Complications		
Spo_2, mean (SD), %	96.3 (1.9)	96.2 (1.9)
≥96%, No. (%)	672 (67.9)	645 (65.3)
91%-95%, No. (%)	309 (31.2)	334 (33.8)
≤90%, No. (%)	8 (0.8)	8 (0.8)
Respiratory infection within the last month, No. (%)	65 (6.6)	56 (5.7)
Anemia, No. (%)[d]	35 (3.5)	26 (2.6)
Planned surgical incision, No. (%)		
Peripheral	126 (12.7)	126 (12.8)
Upper abdominal	863 (87.3)	861 (87.2)
Planned duration of surgery, No. (%)		
2-3 h	671 (67.8)	656 (66.5)
>3 h	318 (32.2)	331 (33.5)
Emergency procedure, No. (%)	21 (2.1)	20 (2.0)
ASA physical status classification, No./total No. (%)[e]		
1 (best health)	15/980 (1.5)	24/976 (2.5)
2	472/980 (48.2)	458/976 (46.9)
3	486/980 (49.6)	487/976 (49.9)
4 (worst health)	7/980 (0.7)	7/976 (0.7)
Cumulative ambulation score, mean (SD)[f]	5.9 (0.5)	5.9 (0.5)
Arterial hypertension, No./total No. (%)	585/988 (59.2)	545/986 (55.3)
Gastroesophageal reflux, No./total No. (%)	332/986 (33.6)	343/986 (34.8)
Diabetes, No./total No. (%)	294/988 (29.7)	291/986 (29.5)
Take oral medication	209/294 (71.0)	198/291 (68.0)
Inject insulin	84/294 (28.6)	73/291 (25.1)
Obstructive sleep apnea, No. (%)	257 (26.0)	264 (26.8)
Tobacco use, No./total No. (%)		
Never	549/987 (55.5)	525/985 (53.2)
Previous	273/987 (27.6)	274/985 (27.8)
Current	165/987 (16.7)	186/985 (18.8)
Use of noninvasive ventilatory support, No. (%)	166 (16.8)	168 (17.0)
Active cancer, No./total No. (%)	110/987 (11.1)	125/986 (12.7)
Chronic obstructive pulmonary disease, No./total No. (%)	52/988 (5.3)	55/986 (5.6)
Use inhalation therapy	37/52 (71.2)	31/55 (56.4)
Take steroids	12/52 (23.1)	11/54 (20.4)

(continued)

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Table 1. Baseline Patient Demographic and Perioperative Characteristics (continued)

Characteristic	High Level of PEEP (n = 989)[a]	Low Level of PEEP (n = 987)[a]
Alcohol use, No. (%)[g]	53 (5.4)	27 (2.7)
Coronary artery disease, No. (%)	37 (3.7)	34 (3.4)
Atrial flutter or fibrillation, No. (%)	37 (3.7)	21 (2.1)
Heart failure, No. (%)	27 (2.7)	29 (2.9)
NYHA heart failure class, No./total No. (%)[h]		
I	6/26 (23.1)	5/28 (17.9)
II	20/26 (76.9)	23/28 (82.1)
Use of medications		
Statins, No. (%)	178 (18.0)	174 (17.6)
Antibiotics within last 3 mo, No./total No. (%)	111/988 (11.2)	123/985 (12.5)
Aspirin, No. (%)	108 (10.9)	106 (10.7)
Preoperative transfusions, No. (%)	4 (0.4)	9 (0.9)
Preoperative vital signs, mean (SD)		
Respiratory rate, breaths/min	15.4 (2.8)	15.5 (2.9)
Heart rate, beats/min	78.6 (12.4)	78.1 (11.8)
Blood pressure, mm Hg	95.8 (13.0)	94.4 (14.1)
Preoperative laboratory tests, mean (SD)		
Hemoglobin, g/dL	13.5 (2.0)	13.7 (1.9)
Creatinine, mg/dL	0.89 (0.6)	0.88 (0.6)
Blood urea nitrogen, mg/dL	21.0 (16.8)	21.2 (18.1)
White blood cells, × 10^9/L	8224 (2346)	8347 (2758)
Preoperative abnormalities on chest radiography, No. (%)	24 (2.4)	31 (3.1)
Antibiotic prophylaxis, No./total No. (%)	938/987 (94.8)	949/985 (96.1)
Type of surgery, No. (%)		
Visceral	777 (78.6)	785 (79.5)
Gynecologic	77 (7.8)	66 (6.7)
Orthopedic	31 (3.1)	28 (2.8)
Urological	20 (2.0)	21 (2.1)
Vascular	13 (1.3)	11 (1.1)
Other	71 (7.2)	76 (7.7)
Surgical approach, No./total No. (%)		
Type of abdominal incision[i]	894/986 (90.7)	884/987 (89.6)
Endoscopic	732/894 (81.9)	721/884 (81.6)
Open	162/894 (18.1)	163/884 (18.4)
Nonabdominal	92/987 (9.3)	102/986 (10.3)
Planned postoperative care in ICU, No. (%)	117 (11.8)	108 (10.9)

Abbreviations: ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA, American Society of Anesthesiology; ICU, intensive care unit; NYHA, New York Heart Association; PEEP, positive end-expiratory pressure; Spo_2, oxygen saturation as measured by pulse oximetry.

SI conversion factors: To convert creatinine to µmol/L, multiply by 88.4.

[a] Some of the characteristics were not assessed in all patients (eg, waist-to-hip ratio).

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

[c] Score range is from 0 to 123; higher scores indicate a higher risk of postoperative pulmonary complications. Patients with scores of 26 or greater are considered at intermediate risk; those with a score greater than 44 are considered at high risk.

[d] Defined as preoperative hemoglobin level of 10 g/dL or less.

[e] Score range is from 1 to 6 and includes a classification for normal health as 1; mild systemic disease, 2; severe systemic disease, 3; severe systemic disease that is a constant threat to life, 4. Patients with scores of 5 or 6 were excluded.

[f] Score range is from 0 to 6; higher scores indicate a higher mobility status.

[g] Defined as more than 2 drinks per day during the past 2 weeks.

[h] Score range is from I to IV; higher scores indicate a higher extent of heart failure. Patients without limitation of their ordinary physical activity are classified NYHA class I; those with slight limitation of their activity are classified as NYHA class II.

[i] Considered as abdominal open (open and conversion) and as abdominal endoscopic (laparoscopic and assisted laparoscopic).

compared with the mean level of 4.0 cm H_2O (SD, 0.5 cm H_2O) in the low level of PEEP group ($P < .001$; eFigure 3 in Supplement 4). In the high level of PEEP group, alveolar recruitment maneuvers were performed in 968 patients (97.9%) after intubation, in 951 patients (96.2%) during the first hour of surgery, and in 968 patients (97.9%) during the last hour of surgery.

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Table 2. Ventilation and Intraoperative Characteristics

Characteristic	High Level of PEEP (n = 989)	Low Level of PEEP (n = 987)	Absolute Difference (95% CI)	*P* Value
Tidal volume, mean (SD), mL/kg of predicted body weight[a]				
After intubation	7.2 (1.4)	7.1 (0.7)	0 (0 to 0.2)	.15
During first hour of surgery	7.2 (1.5)	7.1 (0.4)	0.1 (0 to 0.2)	.007
During last hour of surgery	7.3 (1.6)	7.1 (0.6)	0.1 (0 to 0.2)	.008
PEEP level, mean (SD), cm H_2O				
After intubation	11.5 (2.0)	4.0 (0.7)	7.5 (7.4 to 7.6)	<.001
During first hour of surgery	12.0 (1.1)	4.0 (0.5)	7.9 (7.9 to 8.0)	<.001
During last hour of surgery	12.1 (1.1)	4.1 (0.7)	8.0 (7.9 to 8.1)	<.001
Received alveolar recruitment maneuvers, No. (%)[b]	972 (98.3)	11 (1.1)	97.1 (96.1 to 98.2)	<.001
After intubation	968 (97.9)			
During first hour of surgery	951 (96.2)			
During last hour of surgery	968 (97.9)			
No. of times, median (IQR)	4 (3 to 5)			
Peak pressure, mean (SD), cm H_2O				
After intubation	26.0 (5.0)	23.4 (5.6)	2.6 (2.1 to 3.1)	<.001
During first hour of surgery	27.9 (5.1)	26.5 (5.6)	1.4 (1.0 to 1.9)	<.001
During last hour of surgery	27.5 (5.2)	26.1 (5.7)	1.4 (0.9 to 1.9)	<.001
Driving pressure, mean (SD), cm H_2O[c]				
After intubation	11.3 (4.6)	15.4 (5.1)	−4.1 (−4.5 to −3.6)	<.001
During first hour of surgery	12.2 (4.5)	17.9 (5.4)	−5.7 (−6.1 to −5.2)	<.001
During last hour of surgery	11.8 (4.6)	17.4 (5.4)	−5.6 (−6.0 to −5.1)	<.001
Respiratory rate, mean (SD), breaths/min				
After intubation	14.0 (2.9)	14.4 (2.6)	−0.4 (−0.7 to −0.2)	<.001
During first hour of surgery	16.0 (3.3)	16.2 (3.2)	−0.2 (−0.5 to 0)	.09
During last hour of surgery	17.0 (3.9)	17.4 (3.8)	−0.4 (−0.7 to 0)	.02
F_{IO_2}, mean (SD)				
After intubation	0.57 (0.21)	0.56 (0.20)	0.01 (0 to 0.02)	.27
During first hour of surgery	0.45 (0.09)	0.48 (0.11)	−0.02 (−0.03 to −0.01)	<.001
During last hour of surgery	0.46 (0.11)	0.49 (0.13)	−0.03 (−0.05 to −0.02)	<.001
Spo_2, mean (SD), %				
After intubation	98.2 (2.0)	97.4 (2.5)	0.7 (0.5 to 0.9)	<.001
During first hour of surgery	97.9 (1.9)	96.6 (2.3)	1.3 (1.1 to 1.5)	<.001
During last hour of surgery	98.3 (2.1)	97.1 (2.4)	1.2 (1.0 to 1.4)	<.001
Partial end-tidal CO_2, mean (SD), mm Hg				
After intubation	38.4 (4.8)	38.0 (4.5)	0.3 (0 to 0.8)	.09
During first hour of surgery	40.4 (4.5)	39.9 (4.5)	0.5 (0.1 to 0.9)	.01
During last hour of surgery	41.3 (5.4)	40.6 (5.1)	0.7 (0.2 to 1.1)	.004
Heat rate, mean (SD), beats/min				
After intubation	76.5 (15.8)	76.0 (14.3)	0.6 (−0.7 to 1.9)	.38
During first hour of surgery	72.6 (13.4)	73.1 (14.0)	−0.6 (−1.8 to 0.6)	.36
During last hour of surgery	73.5 (13.0)	74.9 (13.8)	−1.4 (−2.6 to −0.2)	.02
Mean arterial pressure, mean (SD), mm Hg				
After intubation	84.3 (19.3)	82.4 (17.5)	1.8 (0.2 to 3.4)	.03
During first hour of surgery	82.0 (14.9)	81.9 (14.5)	0.1 (−1.2 to 1.4)	.87
During last hour of surgery	81.0 (13.9)	81.1 (13.8)	−0.1 (−1.4 to 1.1)	.81
Angle of head elevation during induction of anesthesia, No. (%)				
0-15°	473 (47.8)	464 (47.0)		.70
>15°	516 (52.2)	523 (53.0)		
Use of noninvasive ventilation, No. (%)	274 (27.7)	264 (26.8)	0.9 (−3.0 to 4.9)	.64

(continued)

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Table 2. Ventilation and Intraoperative Characteristics (continued)

Characteristic	High Level of PEEP (n = 989)	Low Level of PEEP (n = 987)	Absolute Difference (95% CI)	*P* Value
Type of anesthesia, No. (%)				
Total intravenous	104 (10.5)	95 (9.6)		.51
Balanced	885 (89.5)	892 (90.4)		
Epidural analgesia, No. (%)	80 (8.1)	81 (8.2)	−0.1 (−2.5 to 2.3)	.92
Thoracic, No./total No. (%)	64/80 (80.0)	66/81 (81.5)		.81
Lumbar, No./total No. (%)	16/80 (20.0)	15/81 (18.5)		
Neuromuscular blockade, No. (%)	974 (98.5)	961 (97.4)	1.1 (−0.1 to 2.4)	.08
Monitoring of neuromuscular function, No./total No. (%)[d]	632/982 (64.9)	651/984 (67.7)	−1.8 (−6.0 to 2.4)	.40
Reversal, No./total No. (%)	724/982 (74.3)	723/984 (75.2)	0.2 (−3.6 to 4.1)	.90
Total fluids, median (IQR), L	1.5 (1.0 to 2.5)	1.6 (1.0 to 2.5)	0.02 (−0.11 to 0.14)	.79
Crystalloids, median (IQR), L	1.5 (1.0 to 2.5)	1.5 (1.0 to 2.5)	0 (−0.12 to 0.11)	.97
Synthetic colloids				
Median (IQR), L	0.5 (0.5-0.7)	0.5 (0.5-0.5)	0.05 (−0.09 to 0.19)	.50
No. (%)	74 (7.5)	56 (5.7)	1.8 (−0.3 to 4.0)	.09
Urine output, median (IQR), L	0.14 (0 to 0.30)	0.15 (0 to 0.30)	−0.02 (−0.05 to 0.01)	.16
Types of blood products for transfusion, No. (%)				
Packed red blood cells	19 (1.9)	29 (2.9)	−1.0 (−2.3 to 0.3)	.14
Fresh frozen plasma	14 (1.4)	17 (1.7)	−0.3 (−1.4 to 0.7)	.58
Platelets	2 (0.2)	2 (0.2)	0 (−0.3 to 0.3)	>.99
Albumin	19 (1.9)	11 (1.1)	0.8 (−0.2 to 1.8)	.14
Blood loss, mean (SD), mL	187 (412)	182 (382)	5.2 (−30.3 to 40.8)	.77
Temperature at end of surgery, mean (SD), °C	36.3 (0.7)	36.2 (0.7)	0 (0 to 0.1)	.12
Duration, median (IQR), h				
Surgery	2.5 (2.0 to 3.3)	2.5 (2.0 to 3.3)	0 (−0.1 to 0.1)	.62
Anesthesia	3.2 (2.5 to 4.2)	3.2 (2.5 to 4.2)	0 (−0.1 to 0.2)	.94

Abbreviations: CO_2, carbon dioxide; F_{IO_2}, fraction of inspired oxygen; IQR, interquartile range, PEEP, positive end-expiratory pressure; Sp_{O_2}, oxygen saturation as measured by pulse oximetry.

[a] Predicted body weight calculated as 50 + 0.91 × (height in centimeters − 152.4) for men and 45.5 + 0.91 × (height in centimeters − 152.4) for women.

[b] Received any alveolar recruitment maneuvers (ie, maneuvers based on an increase of airway pressure to open atelectatic lung units) during surgery.

[c] Calculated as plateau pressure minus level of PEEP.

[d] Includes any neuromuscular function monitoring (eg, train of 4).

In the low level of PEEP group, alveolar recruitment maneuvers were performed for rescue purposes in 11 patients (1.1%).

Compared with the low level of PEEP group, peak pressure and Sp_{O_2} increased and the driving pressure (ie, plateau pressure minus level of PEEP) and F_{IO_2} decreased in the high level of PEEP group (eFigures 4-7 in Supplement 4). The following did not significantly differ between groups: need for fluids, transfusion of blood products, characteristics of anesthesia, use of epidural analgesia, management of neuromuscular blockade, duration of surgery, and duration of anesthesia. Postoperative pain and dyspnea were comparable between groups (eTable 7 in Supplement 4).

Primary Outcome

Postoperative pulmonary complications within the first 5 days following surgery occurred in 211 patients (21.3%) in the high level of PEEP group compared with 233 patients (23.6%) in the low level of PEEP group (difference, −2.3% [95% CI, −5.9% to 1.4%]; RR, 0.93 [95% CI, 0.83 to 1.04]; *P* = .23) (**Table 3**; eFigure 8 in Supplement 4). The most common postoperative pulmonary complication was mild respiratory failure, which was reported in 135 patients (13.7%) in the high level of PEEP group compared with 154 patients (15.6%) in the low level of PEEP group (difference, −1.9% [95% CI, −5.1% to 1.2%]; RR, 0.92 [95% CI, 0.80 to 1.05]; *P* = .22).

Pleural effusion occurred in 43 patients (4.3%) in the high level of PEEP group compared with 21 patients (2.1%) in the low level of PEEP group (difference, 2.2% [95% CI, 0.7%-3.8%]; RR, 1.35 [95% CI, 1.14-1.62]; *P* = .005). The rates of the other components of the primary end point did not significantly differ between the groups. The effect of PEEP level on the occurrence of postoperative pulmonary complications was consistent across subgroups (**Figure 2**), including nonlaparoscopic vs laparoscopic surgery, body mass index less than 40 vs 40 or greater, baseline Sp_{O_2} less than 96% vs 96% or greater, peripheral vs upper abdominal incision procedures, and waist-to-hip ratio less than 1.0 vs 1.0 or greater.

Secondary Outcomes

Postoperative secondary outcomes appear in Table 3 and in eFigures 9-11 in Supplement 4. Severe postoperative pulmonary complications, postoperative extrapulmonary complications, unexpected admission to the intensive care unit, the number of hospital-free days at day 90, and mortality during

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Table 3. Primary, Secondary, and Post Hoc Outcomes

	No. of Events (%)				
	High Level of PEEP (n = 989)[a]	Low Level of PEEP (n = 987)[a]	Absolute Difference (95% CI), %	Risk Ratio (95% CI)[b]	*P* Value[c]
Primary Outcome					
Postoperative pulmonary complications	211 (21.3)	233 (23.6)	−2.3 (−5.9 to 1.4)	0.93 (0.83 to 1.04)	.23
Components of the Primary Outcome					
Respiratory failure[d]					
Mild	135 (13.7)	154 (15.6)	−1.9 (−5.1 to 1.2)	0.92 (0.80 to 1.05)	.22
Moderate	42 (4.2)	58 (5.9)	−1.6 (−3.6 to 0.3)	0.83 (0.65 to 1.05)	.10
Severe	30 (3.0)	36 (3.6)	−0.6 (−2.2 to 1.0)	0.90 (0.69 to 1.18)	.45
Atelectasis	44 (4.4)	55 (5.6)	−1.1 (−3.0 to 0.8)	0.88 (0.70 to 1.10)	.25
Pleural effusion	43 (4.3)	21 (2.1)	2.2 (0.7 to 3.8)	1.35 (1.14 to 1.62)	.005
New pulmonary infiltrates	14 (1.4)	18 (1.8)	−0.4 (−1.5 to 0.7)	0.87 (0.59 to 1.29)	.47
Cardiopulmonary edema	17 (1.7)	9 (0.9)	0.8 (−0.2 to 1.8)	1.31 (0.99 to 1.74)	.12
Bronchospasm	12 (1.2)	10 (1.0)	0.2 (−0.7 to 1.1)	1.09 (0.74 to 1.60)	.67
Pulmonary infection	10 (1.0)	10 (1.0)	0 (−0.9 to 0.9)	0.99 (0.64 to 1.55)	>.99
Aspiration pneumonitis	2 (0.2)	1 (0.1)	0.1 (−0.2 to 0.4)	1.33 (0.60 to 2.97)	>.99
Acute respiratory distress syndrome	3 (0.3)	1 (0.1)	0.2 (−0.2 to 0.6)	1.50 (0.85 to 2.64)	.62
Pneumothorax	1 (0.1)	3 (0.3)	−0.2 (−0.6 to 0.2)	0.50 (0.09 to 2.72)	.37
Secondary Outcomes					
Severe postoperative pulmonary complications	116 (11.7)	134 (13.6)	−1.8 (−4.8 to 1.1)	0.91 (0.80 to 1.05)	.22
Postoperative extrapulmonary complications	167 (16.9)	150 (15.2)	1.7 (−1.5 to 4.9)	1.06 (0.95 to 1.19)	.31
Systemic inflammatory response syndrome	93 (9.4)	83 (8.4)	1.0 (−1.5 to 3.5)	1.06 (0.91 to 1.22)	.44
Sepsis	18 (1.8)	15 (1.5)	0.3 (−0.8 to 1.4)	1.09 (0.79 to 1.49)	.60
Severe sepsis	7 (0.7)	10 (1.0)	−0.3 (−1.1 to 0.5)	0.82 (0.46 to 1.45)	.46
Septic shock	7 (0.7)	8 (0.8)	−0.1 (−0.9 to 0.7)	0.93 (0.54 to 1.60)	.79
Gastrointestinal failure[e]	65 (6.6)	56 (5.7)	0.9 (−1.2 to 3.0)	1.07 (0.90 to 1.28)	.40
1 (less severe)[f]	34/49 (69.4)	26/46 (56.5)			.64
2[f]	11/49 (22.4)	16/46 (34.8)			
3[f]	3/49 (6.1)	2/46 (4.3)			
4 (more severe)[f]	1/49 (2.0)	2/46 (4.3)			
Acute kidney failure[g]	31 (3.1)	32 (3.2)	−0.1 (−1.6 to 1.4)	0.98 (0.76 to 1.26)	.89
Risk[f]	13/31 (41.9)	15/32 (46.9)			.97
Injury[f]	9/31 (29.0)	10/32 (31.2)			
Failure[f]	7/31 (22.5)	5/32 (15.6)			
Loss[f]	2/31 (6.4)	2/32 (6.2)			
Extrapulmonary infection	29 (2.9)	23 (2.3)	0.6 (−0.8 to 2.0)	1.11 (0.87 to 1.42)	.40
Hepatic failure	9 (0.9)	9 (0.9)	0 (−0.8 to 0.8)	0.99 (0.63 to 1.59)	>.99
Coma	2 (0.2)	2 (0.2)	0 (−0.4 to 0.4)	0.99 (0.37 to 2.66)	>.99
Disseminated intravascular coagulation	1 (0.1)	0	0.1 (−0.1 to 0.3)	2.00 (1.91 to 2.09)	>.99
Acute myocardial infarction	0	0			
Impaired postoperative wound healing	22 (2.2)	26 (2.6)	−0.4 (−1.8 to 0.9)	0.91 (0.66 to 1.24)	.55
Unexpected need for ICU admission or readmission	41 (4.1)	32 (3.2)	0.9 (−0.8 to 2.6)	1.12 (0.91 to 1.38)	.29
Hospital-free days at postoperative day 90					
Mean (SD)	81.2 (16.5)	82.0 (14.5)	−0.77 (−2.16 to 0.61)	−0.77 (−2.16 to 0.61)[h]	.27
Median (IQR)	86 (84 to 87)	86 (84 to 87)			
Intraoperative adverse events					
Hypoxemia[i]	49 (5.0)	134 (13.6)	−8.6 (−11.1 to −6.1)	0.51 (0.40 to 0.65)	<.001
Hypotension[j]	313 (31.6)	170 (17.2)	14.4 (10.7 to 18.2)	1.43 (1.31 to 1.56)	<.001
Bradycardia[k]	98 (9.9)	59 (6.0)	3.9 (1.5 to 6.3)	1.27 (1.11 to 1.45)	.001
Mortality during hospital stay	12 (1.2)	5 (0.5)	0.7 (−0.1 to 1.5)	1.41 (0.95 to 1.81)	.09

(continued)

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Table 3. Primary, Secondary, and Post Hoc Outcomes (continued)

	No. of Events (%)				
	High Level of PEEP (n = 989)[a]	Low Level of PEEP (n = 987)[a]	Absolute Difference (95% CI), %	Risk Ratio (95% CI)[b]	*P* Value[c]
Post Hoc Outcomes					
Intraoperative adverse events					
Rescue strategy for desaturation	59 (6.0)	166 (16.8)	−10.8 (−13.6 to −8.1)	0.49 (0.39 to 0.62)	<.001
Need for vasoactive drugs	491 (49.6)	439 (44.5)	5.2 (0.8 to 9.6)	1.10 (1.01 to 1.21)	.02
Mortality at 5 d	5 (0.5)	3 (0.3)	0.2 (−0.3 to 0.8)	HR, 1.67 (0.40 to 6.97)[l]	.48

Abbreviations: HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; PEEP, positive end-expiratory pressure.

[a] Number of reference patients unless otherwise indicated.

[b] Data are risk ratios unless otherwise indicated. The risk ratios and 95% CIs were calculated using the Wald likelihood ratio approximation test.

[c] Calculated using the χ^2 test.

[d] Defined as an arterial partial pressure of oxygen less than 60 mm Hg or peripheral oxygen saturation as measured by pulse oximetry (Spo_2) less than 90% while breathing at least 10 minutes of room air (beach chair position), excluding hypoventilation. Patients responding to 2 L or less of supplemental oxygen were classified as having mild failure; responding only to greater than 2 L of oxygen, moderate failure. Severe respiratory failure was further defined as the need for noninvasive or invasive mechanical ventilation.

[e] Classified from 1 to 4; higher values indicate a more severe condition. A score of 1 reflects enteral feeding with less than 50% of calculated needs or no feeding 3 days after abdominal surgery; score of 2, food intolerance or intra-abdominal hypertension; score of 3, food intolerance and intra-abdominal hypertension; score of 4, abdominal compartment syndrome.

[f] Data are expressed as No./total No. (%).

[g] Classified in 4 categories according to the stage of kidney injury. Acute kidney failure risk defined as an increase in creatinine level 1.5 times the upper limit of normal, decrease in glomerular filtration rate greater than 25%, or urine output less than 0.5 mL/kg/h for 6 hours; injury, an increase in creatinine level 2 times the upper limit of normal, decrease in glomerular filtration rate greater than 50%, or urine output less than 0.5 mL/kg/h for 12 hours; failure, an increase in creatinine level 3 times the upper limit of normal, decrease in glomerular filtration rate greater than 75%, urine output less than 0.3 mL/kg/h for 24 hours, or anuria for 12 hours; loss, complete loss of kidney function for longer than 4 weeks.

[h] Effect estimate is expressed as the mean difference. The accompanying *P* value was calculated using the *t* test.

[i] Defined as Spo_2 of 92% or less; or any decline in Spo_2 greater than 5% if Spo_2 was previously less than 92%.

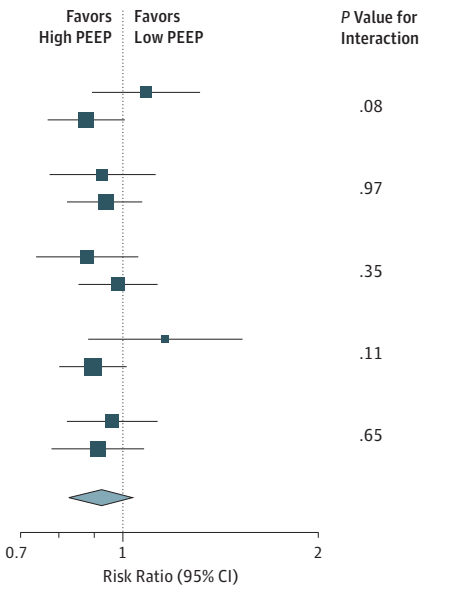
[j] Defined as systolic blood pressure less than 90 mm Hg or any decrease in systolic blood pressure greater than 10 mm Hg if systolic blood pressure was previously less than 90 mm Hg.

[k] Defined as a heart rate less than 50 beats/min or any decrease in heart rate greater than 20% if the heart rate was previously less than 50 beats/min.

[l] The 95% CI and the accompanying *P* value were calculated using the Cox proportional hazards model.

Figure 2. Risk Ratio for Postoperative Pulmonary Complications (PPCs) in Prespecified Subgroups

Subgroups of Patients	High PEEP No. With PPC	High PEEP Total No.	Low PEEP No. With PPC	Low PEEP Total No.	Risk Ratio (95% CI)	*P* Value for Interaction
Type of surgery						
Nonlaparoscopic	79	240	74	253	1.09 (0.90-1.32)	.08
Laparoscopic	130	740	156	727	0.88 (0.77-1.01)	
Body mass index[a]						
<40	76	336	94	376	0.93 (0.77-1.13)	.97
≥40	135	653	139	611	0.94 (0.82-1.08)	
Peripheral oxygen saturation, %						
<96	88	317	112	342	0.88 (0.74-1.06)	.35
≥96	123	672	121	645	0.99 (0.86-1.13)	
Type of incision						
Peripheral	32	126	25	126	1.16 (0.89-1.53)	.11
Upper abdominal	179	863	208	861	0.90 (0.80-1.02)	
Waist-to-hip ratio, cm						
<1.0	97	467	100	457	0.97 (0.83-1.13)	.65
≥1.0	98	447	112	449	0.92 (0.78-1.08)	
All patients	211	989	233	987	0.93 (0.83-1.04)	



The data marker sizes are proportional to the numbers of patients entering the analysis. PEEP indicates positive end-expiratory pressure.

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

hospital stay did not significantly differ between groups. During the intraoperative period, hypoxemia was less common in the high level of PEEP group, and hypotension and bradycardia were less frequent in the low level of PEEP group.

Additional Analysis

The results of the per-protocol and the intention-to-treat analysis did not significantly differ (eTable 8 in Supplement 4). The results were unaffected by adjustment for randomization

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factors (eTable 9 in Supplement 4). Additional sensitivity analyses using different statistical assumptions yielded similar results (eTable 9 and eFigure 12 in Supplement 4).

Post Hoc Analyses

During the intraoperative period, post hoc analyses showed that the need for a rescue strategy for desaturation was less common in the high level of PEEP group, whereas in the low level of PEEP group, the need for vasoactive drugs was lower (Table 3). In addition, 5-day mortality did not significantly differ between groups.

Discussion

Among obese patients undergoing surgery, intraoperative mechanical ventilation with a high level of PEEP and alveolar recruitment maneuvers did not reduce postoperative pulmonary complications compared with a low level of PEEP. During the intraoperative period, hypotension was more frequent in patients randomized to the high level of PEEP group, whereas hypoxemia was more common in patients randomized to the low level of PEEP group.

Use of an intraoperative high level of PEEP and alveolar recruitment maneuvers may prevent the development of lung atelectasis,[22] decrease the driving pressure,[23] homogenize ventilation,[15] and minimize the repetitive opening and closing of lung units, which could mitigate the development of pulmonary complications.[24] However, use of a high level of PEEP and alveolar recruitment maneuvers can also have adverse effects, including increased static stress and strain,[25] inflammation,[26] impaired hemodynamics,[11] and decreased lung lymphatic drainage.[27]

The choice of a PEEP level of 4 cm H_2O in the low level of PEEP group was based on data that was already available when the study was designed.[3] Because a PEEP level of 4 cm H_2O was unlikely to provide enough stability for a substantial proportion of lung units being kept open after alveolar recruitment maneuvers, such maneuvers were not routinely performed in that group. The design of the intervention in the high level of PEEP group was consistent with the concept of increasing the availability of lung units for gas exchange and stabilizing them at expiration, while limiting the effect on hemodynamics.[22] For this reason, but also because chest wall elastance may increase during surgery, alveolar recruitment maneuvers were repeated at intervals of 1 hour in the high level of PEEP group.

Previous studies reported that PEEP and alveolar recruitment maneuvers improved intraoperative pulmonary function.[15,22] However, those studies were inadequately powered to address postoperative pulmonary complications. The finding of the present study that ventilation with a higher level of PEEP and alveolar recruitment maneuvers did not reduce postoperative pulmonary complications is consistent with results among normal weight patients who underwent abdominal surgery, in whom high levels of PEEP with alveolar recruitment maneuvers also did not prevent postoperative pulmonary complications.[11,12] Taken together, evidence from major trials indicates that intraoperative mechanical ventilation strategies aiming to reduce atelectasis do not prevent postoperative pulmonary complications compared with a strategy allowing higher degrees of atelectasis (also known as permissive atelectasis).

The finding that intraoperative hypotension and bradycardia were more frequent in patients randomized to higher levels of PEEP is consistent with previous reports among obese patients undergoing bariatric surgery[15] and among normal weight patients undergoing abdominal surgery.[11] Theoretically, preoperative optimization of intravascular volume might have decreased hemodynamic adverse events. However, this practice is not universally accepted in surgical patients, and given the pragmatic nature of this trial, it was not recommended to be incorporated at the sites. In addition, the observation that hypoxemia occurred more frequently and the rescue strategy for desaturation was needed more often in the lower level of PEEP group is consistent with recent findings from patients who underwent bariatric surgery, had lung reexpansion, and individual titration of PEEP[15] and among normal weight and overweight patients.[11,12]

Therefore, the data from the present study confirm that intraoperative PEEP exerts concurring effects on lung function and circulation. A decrease in the driving pressure among patients in the higher level of PEEP group compared with the lower level of PEEP group did not result in improved clinical outcome measures, which was expected based on previous studies involving patients with acute respiratory distress syndrome[28] and conducted in the operating room.[8,29] However, such studies were not interventional, suggesting that the driving pressure is a reliable marker for clinical outcome; however, its usefulness as a therapeutic target is still unclear.

The observed incidence of postoperative pulmonary complications was within the range predicted by the Assess Respiratory Risk in Surgical Patients in Catalonia score and comparable with that reported in a previous study focusing on intraoperative mechanical ventilation in obese patients.[1] Mild respiratory failure was the most frequent pulmonary complication and also was reported in several studies addressing the incidence of postoperative pulmonary complications.[1-4,11,18] Mild respiratory failure was associated with prolonged hospitalization and mortality in the general population[4] and in obese patients undergoing surgery[1]; therefore, it is clinically important.

The overall incidence of pleural effusion was lower than in a previous trial in normal weight and overweight patients,[11] but was higher in the higher level of PEEP group compared with the lower level of PEEP group. In a ventilatory strategy with high levels of PEEP, increased hydrostatic forces across the lung capillaries (associated with raised venous pressures and impaired lymphatic drainage) may result in interstitial fluid sequestration.[30] Given comparable rates of postoperative pulmonary complications, clinicians can titrate intraoperative PEEP level to optimize oxygenation or to maintain blood pressure as indicated in particular patients.

This study has several strengths. A composite outcome of postoperative pulmonary complications was selected because

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the complications have been associated with prolonged hospitalization and increased mortality. The interventions were based on the current practice in the lower level of PEEP group,[1] and on recommendations for clinical practice in the higher level of PEEP group.[13,16] Bias was minimized by using concealed allocation, blinding of outcome assessors, an intention-to-treat analysis, and avoiding loss to follow-up. The sample size was readjusted after a recommendation from the data and safety monitoring committee, maintaining the power to detect clinically significant differences between the groups.

Additional strengths of this trial were that patients were enrolled during a relatively short period, minimizing the influence of changes in clinical practice. Furthermore, patients were enrolled at 77 sites in 23 countries and several types of surgery were included. The present results are thus generalizable.

Limitations

This study has several limitations. First, intraoperative anesthesiologists could not be blinded to the interventions. However, patients and postoperative assessors were fully blinded to the intraoperative period.

Second, the alveolar recruitment maneuver was based on stepwise increases in tidal volume, which is accompanied by transient increases in the driving pressure. How best to perform alveolar recruitment maneuvers during anesthesia remains unclear, but it is unlikely that results would differ with an alternative approach.

Third, because the trial was pragmatic, individual titration of PEEP level was not attempted. In obese patients undergoing surgery, a PEEP level of 10 cm H_2O for open surgery and of 14 cm H_2O for laparoscopic surgery represent a reasonable compromise between lung overdistension and collapse.[31] A PEEP level of 12 cm H_2O in the higher level of PEEP group was chosen as a compromise.

Fourth, respiratory management during emergence and during the immediate postoperative period was not harmonized among sites, but recommendations were given following international standards. Nevertheless, the results of the present study still apply only to intraoperative ventilation management.

Fifth, the composite outcome of postoperative pulmonary complications included events with different degrees of severity. However, even so-called minor pulmonary complications are associated with clinically relevant outcomes.

Sixth, it was not possible to differentiate upper from lower abdominal incisions, which may be associated with different degrees of pulmonary complications. However, in an analysis of patients who underwent abdominal visceral surgery, the interaction between the surgical approach (ie, open vs laparoscopic) was not significant.

Conclusions

Among obese patients undergoing surgery under general anesthesia, an intraoperative mechanical ventilation strategy with a higher level of PEEP and alveolar recruitment maneuvers, compared with a strategy with a lower level of PEEP, did not reduce postoperative pulmonary complications.

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