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ORIGINAL ARTICLE

A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery

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ABSTRACT

BACKGROUND

Lung-protective ventilation with the use of low tidal volumes and positive end-expiratory pressure is considered best practice in the care of many critically ill patients. However, its role in anesthetized patients undergoing major surgery is not known.

METHODS

In this multicenter, double-blind, parallel-group trial, we randomly assigned 400 adults at intermediate to high risk of pulmonary complications after major abdominal surgery to either nonprotective mechanical ventilation or a strategy of lung-protective ventilation. The primary outcome was a composite of major pulmonary and extrapulmonary complications occurring within the first 7 days after surgery.

RESULTS

The two intervention groups had similar characteristics at baseline. In the intention-to-treat analysis, the primary outcome occurred in 21 of 200 patients (10.5%) assigned to lung-protective ventilation, as compared with 55 of 200 (27.5%) assigned to nonprotective ventilation (relative risk, 0.40; 95% confidence interval [CI], 0.24 to 0.68; P=0.001). Over the 7-day postoperative period, 10 patients (5.0%) assigned to lung-protective ventilation required noninvasive ventilation or intubation for acute respiratory failure, as compared with 34 (17.0%) assigned to nonprotective ventilation (relative risk, 0.29; 95% CI, 0.14 to 0.61; P=0.001). The length of the hospital stay was shorter among patients receiving lung-protective ventilation than among those receiving nonprotective ventilation (mean difference, −2.45 days; 95% CI, −4.17 to −0.72; P=0.006).

CONCLUSIONS

As compared with a practice of nonprotective mechanical ventilation, the use of a lung-protective ventilation strategy in intermediate-risk and high-risk patients undergoing major abdominal surgery was associated with improved clinical outcomes and reduced health care utilization. (IMPROVE ClinicalTrials.gov number, NCT01282996.)

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Worldwide, more than 230 million patients undergoing major surgery each year require general anesthesia and mechanical ventilation.[1] Postoperative pulmonary complications adversely affect clinical outcomes and health care utilization,[2] so prevention of these complications has become a measure of the quality of hospital care.[3] Previous, large cohort studies have shown that 20 to 30% of patients undergoing surgery with general anesthesia are at intermediate to high risk for postoperative pulmonary complications.[4,5]

Mechanical ventilation with the use of high tidal volumes (10 to 15 ml per kilogram of predicted body weight) has traditionally been recommended to prevent hypoxemia and atelectasis in anesthetized patients.[6] There is, however, considerable evidence from experimental and observational studies that mechanical ventilation — in particular, high tidal volumes that cause alveolar overstretching — can initiate ventilator-associated lung injury[7] and contribute to extrapulmonary organ dysfunction through systemic release of inflammatory mediators.[8,9]

Lung-protective ventilation, which refers to the use of low tidal volumes and positive end-expiratory pressure (PEEP), and which may also include the use of recruitment maneuvers (periodic hyperinflation of the lungs),[10] has been shown to reduce mortality among patients with the acute respiratory distress syndrome[11] and is now considered best practice in the care of many critically ill patients.[12] Although this approach may be beneficial in a broader population,[13,14] some physicians have questioned the benefits of using lung-protective ventilation in the surgical setting,[15-18] especially since the use of high tidal volumes and no PEEP is still commonplace and less than 20% of patients receive protective ventilation in routine anesthetic practice.[19,20]

We conducted the Intraoperative Protective Ventilation (IMPROVE) trial to determine whether a multifaceted strategy of prophylactic lung-protective ventilation that combined low tidal volumes, PEEP, and recruitment maneuvers could improve outcomes after abdominal surgery, as compared with the standard practice of nonprotective mechanical ventilation.

METHODS

TRIAL DESIGN AND OVERSIGHT

The IMPROVE trial was an investigator-initiated, multicenter, double-blind, stratified, parallel-group, clinical trial. Randomization was performed with the use of a computer-generated assignment sequence and a centralized telephone system. The study protocol and statistical analysis plan were approved for all centers by a central ethics committee (Comité de Protection des Personnes Sud-Est I, Saint-Etienne, France) according to French law. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. An independent data and safety monitoring committee oversaw the study conduct and reviewed blinded safety data. The members of the steering committee (see the Supplementary Appendix, available at NEJM.org) vouch for the accuracy and completeness of the data and analyses and the fidelity of the study to the protocol. There was no industry support or involvement in the trial.

Patients were screened and underwent randomization between January 31, 2011, and August 10, 2012, at seven French university teaching hospitals. Written informed consent was obtained before randomization from each patient, on the day before surgery. Randomization was stratified according to study site and the planned use or nonuse of postoperative epidural analgesia, which is a factor that may influence outcomes.[21] Treatment assignments were concealed from patients, research staff, the statistician, and the data and safety monitoring committee. Although the staff members who collected data during surgery were aware of the group assignments, outcome assessors were unaware of these assignments throughout the study.

PATIENTS

Patients were eligible for participation in the study if they were older than 40 years of age, were scheduled to undergo laparoscopic or nonlaparoscopic elective major abdominal surgery[1] with an expected duration of at least 2 hours, and had a preoperative risk index for pulmonary complications[5] of more than 2. The risk index uses risk classes that range from 1 to 5, with higher risk classes indicating a higher risk of postoperative pulmonary complications (see the

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Supplementary Appendix). Patients were ineligible if they had received mechanical ventilation within the 2 weeks preceding surgery, had a body-mass index (the weight in kilograms divided by the square of the height in meters) of 35 or higher, had a history of respiratory failure or sepsis within the 2 weeks preceding surgery, had a requirement for intrathoracic or emergency surgery, or had a progressive neuromuscular illness.

INTERVENTIONS

Patients were assigned to receive volume-controlled mechanical ventilation according to one of two strategies: nonprotective ventilation with a tidal volume of 10 to 12 ml per kilogram of predicted body weight, with no PEEP and no recruitment maneuvers, as previously described[20] (the nonprotective-ventilation group), or lung-protective ventilation with a tidal volume of 6 to 8 ml per kilogram of predicted body weight, a PEEP of 6 to 8 cm of water, and recruitment maneuvers repeated every 30 minutes after tracheal intubation (the protective-ventilation group). Each recruitment maneuver consisted of applying a continuous positive airway pressure of 30 cm of water for 30 seconds. During anesthesia, a plateau pressure of no more than 30 cm of water was targeted in each group. All other ventilation procedures were identical in the two study groups (see the Supplementary Appendix).

The predicted body weight was calculated for each patient with the use of previously defined formulas.[11] For episodes of arterial desaturation (defined as a peripheral oxygen saturation of ≤92%), a transient increase in the fraction of inspired oxygen (FIO_2) to 100% was permitted, and in patients assigned to nonprotective ventilation, the use of PEEP, recruitment maneuvers, or both was allowed, if required. Decisions about all other aspects of patient care during the intraoperative and postoperative periods, including general anesthesia, administration of fluids, use of prophylactic antibiotic agents, and postoperative pain management, were made by the attending physician according to the expertise of the staff at each center and routine clinical practice.

OUTCOMES

The primary outcome was a composite of major pulmonary and extrapulmonary complications occurring by day 7 after surgery. Major pulmonary complications were defined as pneumonia (defined according to standard criteria; see the Supplementary Appendix) or the need for invasive or noninvasive ventilation for acute respiratory failure. Major extrapulmonary complications were defined as sepsis, severe sepsis and septic shock (defined according to consensus criteria),[22] or death.

Secondary outcomes within the 30-day follow-up period were the incidence of pulmonary complications due to any cause, graded on a scale from 0 (no pulmonary complications) to 4 (the most severe complications)[23] (see the Supplementary Appendix); ventilation-related adverse events during surgery; postoperative gas exchange; unexpected need for admission to the intensive care unit (ICU); extrapulmonary complications; durations of ICU and hospital stays; and the rate of death from any cause 30 days after surgery. Pulmonary complications were analyzed separately; in particular, the need for invasive or noninvasive ventilation because of acute respiratory failure, the development of postoperative atelectasis, pneumonia, acute lung injury, and the acute respiratory distress syndrome, defined according to standard criteria (see the Supplementary Appendix). Extrapulmonary complications included the systemic inflammatory response syndrome (SIRS); sepsis; severe sepsis and septic shock; and surgical complications, including intraabdominal abscess, anastomotic leakage, and unplanned reoperation (all defined according to consensus criteria[22,24]).

STATISTICAL ANALYSIS

We calculated that a sample of 400 patients would provide 80% power to detect a relative difference of 50% in the primary outcome, at a two-sided alpha level of 0.05, assuming a 20% rate of postoperative complications in the nonprotective-ventilation group.[25] For safety reasons, an interim analysis was conducted after the enrollment of the first 200 patients, according to the a priori statistical analysis plan. The data and safety monitoring committee did not recommend discontinuation of the trial on the basis of that analysis, and 400 patients were therefore included. A total of 3 patients were excluded after randomization; surgery was stopped prematurely in 2 of the 3 patients because of extensive illness (duration of surgery, <2 hours), and 1 had undergone randomization in error (violation of exclusion criteria). An additional 3 patients were thus randomly assigned to a study group to obtain the full sample.

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All analyses were conducted on data from the modified intention-to-treat population, which included all patients who underwent randomization except the three who were excluded (Fig. 1). An unadjusted chi-square test was used for the primary outcome analysis. Multiple logistic-regression analysis was used to identify relevant baseline covariates associated with the primary outcome, in addition to the stratification variables (use or nonuse of epidural analgesia and study center). Variables tested in the model were selected if the P value was less than 0.10 and if they were clinically relevant. Adjusted analyses were performed with the use of robust Poisson generalized-linear-model regression[26] and are presented as relative risks with 95% confidence intervals. A chi-square test (or Fisher's exact test, as appropriate) was used for secondary binary outcomes. The Hochberg procedure was used to adjust for multiple testing of components of the composite primary outcome.[27] Adjusted analyses were performed with the use of the same adjustment variables that were used in the robust Poisson regression analysis. Continuous variables were compared with the use of an unpaired t-test or the Mann–Whitney U test. Adjusted analyses were performed with the use

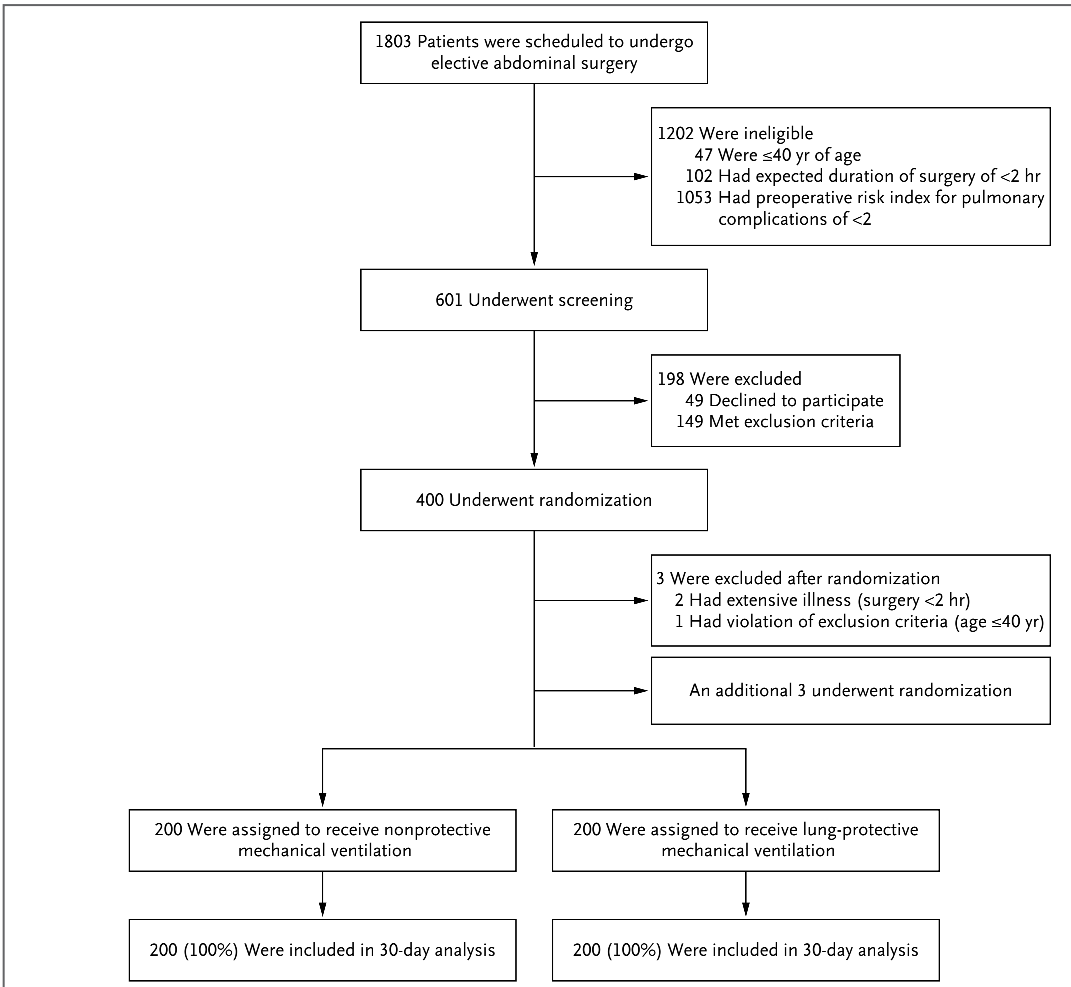

Figure 1. Assessment, Randomization, and Follow-up of Patients.

A total of 1803 patients awaiting abdominal surgery were assessed preoperatively for trial eligibility by the research staff. A total of 400 patients were included in the modified intention-to-treat analysis and were followed for 30 days after surgery. After randomization, 3 patients were excluded; 2 patients were excluded because surgery was stopped prematurely (duration, <2 hours), owing to extensive illness, and 1 had undergone randomization in error. An additional 3 patients were then enrolled in the study.

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Nonprotective Ventilation (N=200)	Lung-Protective Ventilation (N=200)
Age — yr	63.4±10.0	61.6±11.0
Male sex — no. (%)	121 (60.5)	116 (58.0)
Height — cm	169.5±9.0	169.1±8.8
Body weight — kg		
Actual	71.3±13.9	71.4±14.2
Predicted†	63.8±9.9	63.3±9.7
Body-mass index‡		
Mean	24.7±3.8	24.8±3.8
25–35 — no. (%)	88 (44.0)	99 (49.5)
Preoperative risk index — no. (%)§		
Risk class 2	100 (50.0)	101 (50.5)
Risk class 3	94 (47.0)	93 (46.5)
Risk class 4 or 5	6 (3.0)	6 (3.0)
Coexisting condition — no. (%)¶		
Current smoking	50 (25.0)	51 (25.5)
Any alcohol intake	10 (5.0)	21 (10.5)
Not fully independent in activities of daily living	8 (4.0)	8 (4.0)
Chronic obstructive pulmonary disease	20 (10.0)	20 (10.0)
Loss of >10% of body weight in previous 6 mo	44 (22.0)	40 (20.0)
Long-term glucocorticoid use	4 (2.0)	7 (3.5)
Laparoscopic surgery — no. (%)	44 (22.0)	41 (20.5)
Type of surgery — no. (%)		
Pancreaticoduodenectomy	80 (40.0)	84 (42.0)
Liver resection	52 (26.0)	44 (22.0)
Gastrectomy	17 (8.5)	15 (7.5)
Colorectal resection	40 (20.0)	47 (23.5)
Other procedure	11 (5.5)	10 (5.0)
Diagnosis — no. (%)		
Cancer	164 (82.0)	155 (77.5)
Diagnosis other than cancer	36 (18.0)	45 (22.5)

* Plus–minus values are means ±SD. There were no significant differences between the two groups (P>0.05).
† The predicted body weight was calculated as follows: for men, 50+0.91(height in centimeters − 152.4); and for women, 45.5 + 0.91(height in centimeters − 152.4).[11]
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The preoperative risk index for pulmonary complications[5] uses risk classes that range from 1 to 5, with higher risk classes indicating a higher risk of postoperative complications. Patients with a risk class of 2 or more were eligible for participation in the study.
¶ All factors listed as coexisting conditions were included in the preoperative risk index as predictors of postoperative pulmonary complications.

of the same adjustment variables that were used in the linear-regression model. The time-to-event curves were calculated with the Kaplan–Meier method. Details regarding the handling of missing data are provided in the Supplementary Appendix.

All analyses were conducted with the use of Stata software, version 12 (StataCorp). A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATION

From January 2011 through August 2012, a total of 1803 patients awaiting abdominal surgery were assessed for trial eligibility. A total of 400 patients were included in the modified intention-to-treat analysis and were followed for 30 days after surgery (Fig. 1). One patient in the nonprotective-ventilation group received lung-protective ventilation but was included in the analysis for the group to which he was assigned. Data on the primary outcome were available for all patients. Baseline characteristics were similar between the two groups (Table 1). Open laparotomy, mainly for cancer resection, was performed in 156 patients (78.0%) in the nonprotective-ventilation group and in 159 (79.5%) in the protective-ventilation group (P=0.80).

INTRAOPERATIVE PROCEDURES

Table 2 shows the distribution of the main intraoperative procedures. Mean (±SD) tidal volumes were 11.1±1.1 ml per kilogram in the nonprotective-ventilation group, as compared with 6.4±0.8 ml per kilogram in the protective-ventilation group (P<0.001), and values remained within target ranges throughout the intraoperative period. In the protective-ventilation group, the median PEEP was 6 cm of water (interquartile range, 6 to 8), and the median number of recruitment maneuvers was 9 (interquartile range, 6 to 12); in the nonprotective-ventilation group, the value for each of these measures was 0 (interquartile range, 0 to 0) (Table 2). There were no significant between-group differences in type and duration of surgery, use or nonuse of epidural analgesia, blood loss, volume of fluids administered, and need for vasopressor administration. Five patients in the nonprotective-ventilation group required at least one intraoperative rescue therapy for arterial de-

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Table 2. Intraoperative Procedures.*

Variable	Nonprotective Ventilation (N=200)	Lung-Protective Ventilation (N=200)	P Value
Tidal volume — ml	719.0±127.8	406.7±75.6	<0.001
Tidal volume — ml/kg of predicted body weight	11.1±1.1	6.4±0.8	<0.001
PEEP — cm of water			
Baseline			<0.001
Median	0	6	
Interquartile range	0–0	6–8	
End of surgery			<0.001
Median	0	6	
Interquartile range	0–0	6–8	
No. of recruitment maneuvers			<0.001
Median	0	9	
Interquartile range	0–0	6–12	
Peak pressure — cm of water			
Baseline	20.1±4.9	18.9±3.6	0.04
End of surgery	20.6±4.4	20.0±4.0	0.15
Plateau pressure — cm of water			
Baseline	16.1±4.3	15.2±3.0	0.02
End of surgery	16.6±3.5	15.2±2.6	<0.001
Respiratory system compliance — ml/cm of water			
Baseline	48.4±17.8	55.2±26.6	0.06
End of surgery	45.1±12.9	55.2±26.7	<0.001
FiO_2 — %	47.2±7.6	46.4±7.3	0.27
Volume of fluids administered — liters			
Crystalloid			0.47
Median	2.0	1.5	
Interquartile range	1.5–3.5	2.0–3.0	
Colloid			0.97
Median	0.5	0.5	
Interquartile range	0.25–1.0	0.50–1.0	
Duration of surgery — no./total no. (%)†			0.95
2–4 hr	76/192 (39.6)	75/195 (38.5)	
>4–6 hr	75/192 (39.1)	76/195 (39.0)	
>6 hr	41/192 (21.4)	44/195 (22.6)	
Duration of mechanical ventilation — min	344±127.9	319±139.4	0.84
Epidural analgesia — no. (%)	77 (38.5)	83 (41.5)	0.61

* Plus–minus values are means ±SD. Detailed data on intraoperative procedures are given in Table S2 in the Supplementary Appendix. FiO_2 denotes inspired oxygen fraction, and PEEP positive end-expiratory pressure.
† The duration of surgery was calculated as the time between skin incision and closure of the incision.

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saturation (PEEP in one patient, recruitment maneuvers in two, and both in two), as compared with no patients in the protective-ventilation group (P=0.06).

OUTCOMES

Primary Outcome

Major pulmonary and extrapulmonary complications occurred within the first 7 days after surgery in 21 patients (10.5%) in the protective-ventilation group, as compared with 55 (27.5%) in the nonprotective-ventilation group (adjusted relative risk, 0.40; 95% confidence interval [CI], 0.24 to 0.68; P=0.001) (Table 3). The results of associated univariate and multivariate analyses are provided in Table S1 in the Supplementary Appendix.

Secondary Outcomes

One or more pulmonary complications developed within the first 7 days after surgery in 35 patients (17.5%) in the protective-ventilation group, as compared with 72 (36.0%) in the nonprotective-ventilation group (adjusted relative risk, 0.49; 95% CI, 0.32 to 0.74; P<0.001). More patients in the nonprotective-ventilation group than in the protective-ventilation group had major (grade ≥3) pulmonary complications (Table 3, and Tables S3 and S4 in the Supplementary Appendix) and major pulmonary and extrapulmonary complications during the 30 days after surgery (P<0.001 by the log-rank test) (Fig. 2). There were no relevant between-group differences in gas exchange after extubation and on day 1 after surgery (Table S5 in the Supplementary Appendix).

The proportion of patients who required postoperative ventilatory assistance (noninvasive ventilation or intubation) for acute respiratory failure was lower in the protective-ventilation group than in the nonprotective-ventilation group during the first 7 days after surgery (10 of 200 patients [5.0%], vs. 34 of 200 [17.0%]; adjusted relative risk, 0.29; 95% CI, 0.14 to 0.61; P=0.001), and the proportion was also lower with protective ventilation during the first 13 days after surgery (6.5% vs. 18.5%; adjusted relative risk, 0.36; 95% CI, 0.19 to 0.70; P=0.003) (Table 3). In addition, the cumulative 30-day probability of an event requiring intubation or noninvasive ventilation for postoperative acute respiratory failure was lower among patients who received lung-protective ventilation than among those who received nonprotective ventilation (P<0.001 by the log-rank test) (Fig. S1 in the Supplementary Appendix).

There was no significant difference between the protective-ventilation group and the nonprotective-ventilation group with respect to the proportion of patients who were unexpectedly admitted to the ICU during the 30-day period after surgery (11.0 and 12.5%, respectively; adjusted relative risk with protective ventilation, 0.88; 95% CI, 0.49 to 1.59; P=0.67), nor was there a significant between-group difference in the rate of adverse events (Table S3 in the Supplementary Appendix). Mortality at 30 days in the protective-ventilation group was similar to that in the nonprotective-ventilation group (3.0% and 3.5%, respectively; adjusted relative risk with protective ventilation, 1.13; 95% CI, 0.36 to 3.61; P=0.83). However, the median hospital stay was shorter in the protective-ventilation group than in the nonprotective-ventilation group (Table 3).

DISCUSSION

In this trial, intraoperative lung-protective mechanical ventilation, as compared with nonprotective ventilation, led to improved clinical outcomes and reduced health care utilization after abdominal surgery. The observed rate of postoperative complications in our study was slightly higher than predicted.[25] This was due, in part, to the exclusion of patients with a low risk of complications, as well as the large proportion of patients who underwent major abdominal procedures, which are associated with increased morbidity rates. Of the 400 patients enrolled, 19 had postoperative pneumonia and 47 had respiratory failure requiring intubation or noninvasive ventilation. These rates are consistent with previously reported rates of pulmonary complications[25,28] and mortality.[29] Our lung-protective ventilation strategy resulted in a 69% reduction in the number of patients requiring ventilatory support within the first 7 days after surgery.

Several hypotheses could explain some of the differences between the results of the present study and findings in other trials of lung-protective ventilation during high-risk surgery. Previous trials have included small numbers of patients, have focused on different (and not necessarily clinically relevant) outcomes,[17] and

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Table 3. Results of Unadjusted and Adjusted Outcome Analyses.*

Variable	Nonprotective Ventilation (N=200)	Lung-Protective Ventilation (N=200)	Unadjusted Relative Risk or Between-Group Difference (95% CI)	P Value†	Adjusted Relative Risk or Between-Group Difference (95% CI)‡	P Value
Primary composite outcome — no. (%)						
Within 7 days§	55 (27.5)	21 (10.5)	0.38 (0.24–0.61)	<0.001	0.40 (0.24–0.68)	0.001
Within 30 days	58 (29.0)	25 (12.5)	0.43 (0.28–0.66)	<0.001	0.45 (0.28–0.73)	<0.001
Secondary outcomes — no. (%)						
Pulmonary complication within 7 days¶						
Grade 1 or 2	30 (15.0)	25 (12.5)	0.69 (0.42–1.13)	0.14	0.67 (0.39–1.16)	0.16
Grade ≥3	42 (21.0)	10 (5.0)	0.24 (0.12–0.46)	<0.001	0.23 (0.11–0.49)	<0.001
Atelectasis within 7 days‖	34 (17.0)	13 (6.5)	0.38 (0.21–0.70)	0.001	0.37 (0.19–0.73)	0.004
Pneumonia within 7 days	16 (8.0)	3 (1.5)	0.19 (0.05–0.63)	0.01	0.19 (0.05–0.66)	0.009
Acute lung injury or ARDS within 7 days	6 (3.0)	1 (0.5)	0.17 (0.02–1.37)	0.12	0.21 (0.02–1.71)	0.14
Need for ventilation within 7 days						
Invasive	7 (3.5)	2 (1.0)	0.29 (0.06–1.36)	0.51	0.40 (0.08–1.97)	0.26
Noninvasive	29 (14.5)	9 (4.5)	0.31 (0.15–0.64)	0.006	0.29 (0.13–0.65)	0.002
Extrapulmonary complication within 7 days						
SIRS	100 (50.0)	86 (43.0)	0.86 (0.70–1.06)	0.16	0.87 (0.65–1.17)	0.37
Sepsis	29 (14.5)	13 (6.5)	0.45 (0.24–0.84)	0.04	0.48 (0.25–0.93)	0.03
Severe sepsis or septic shock	9 (4.5)	8 (4.0)	0.89 (0.35–2.26)	0.80	1.48 (0.51–4.32)	0.47
Death within 30 days	7 (3.5)	6 (3.0)	0.86 (0.29–2.51)	0.80	1.13 (0.36–3.61)	0.83
Duration of stay in hospital and ICU — days						
Hospital				0.02		0.006
Median	13	11	−2.25 (−4.04 to −0.47)		−2.45 (−4.17 to −0.72)	
Interquartile range	8–20	8–15				
ICU				0.58		0.69
Median	7	6	−1.48 (−6.87 to 3.91)		−1.21 (−4.98 to 7.40)	
Interquartile range	4–9	4–8				

* All postoperative complications were defined according to consensus criteria (see the Supplementary Appendix). For additional data on postoperative outcomes, see Tables S3 and S4 in the Supplementary Appendix. ARDS denotes acute respiratory distress syndrome, CI confidence interval, ICU intensive care unit, and SIRS systemic inflammatory response syndrome. Relative risks are shown for outcome variables, and differences between groups are shown for the duration of stays in the hospital and ICU.
† Adjustment was performed for stratification variables (use or nonuse of epidural analgesia and study center), preoperative risk index for postoperative pulmonary complications, sex, duration of surgery, and need for blood transfusion (yes or no).
‡ The Hochberg procedure was used to adjust for multiple testing of components of the composite primary outcome.[27]
§ The primary outcome was a composite of major pulmonary complications (defined as pneumonia or need for invasive or noninvasive ventilation for acute respiratory failure) and extrapulmonary complications (defined as sepsis, septic shock, or death) within the first 7 days after surgery.
¶ Postoperative pulmonary complications were scored with the use of a graded scale[23] from 0 (no pulmonary complications) to 4 (the most severe complications) (see the Supplementary Appendix).
‖ Atelectasis was defined as opacification of the lung with shift of the mediastinum, hilum, or hemidiaphragm toward the affected area and compensatory overinflation in the adjacent, nonatelectatic lung.

have used either very low levels of PEEP or no PEEP.[15,16,18] One strength of the present trial is our use of a robust composite outcome that is highly pertinent to this high-risk surgical population.[5] Mechanical ventilation itself can induce an inflammatory response[30] and can synergize with the response induced by major surgery at both local and systemic levels. This amplification of

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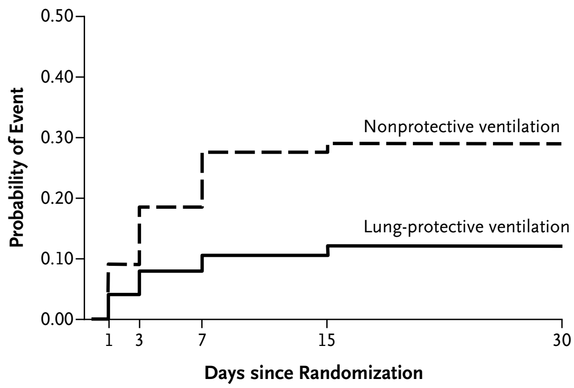

No. at Risk

	1	3	7	15	30	
Nonprotective ventilation	200	182	163	145	142	142
Lung-protective ventilation	200	192	184	179	176	175

Figure 2. Kaplan–Meier Estimates of the Probability of the Composite Primary Outcome.

Data for the Kaplan–Meier estimates of the probability of the composite primary outcome of major pulmonary or extrapulmonary complications were censored at 30 days after surgery. Major pulmonary complications included pneumonia or the need for invasive or noninvasive ventilation for acute respiratory failure. Major extrapulmonary complications were sepsis, severe sepsis, septic shock, and death. $P<0.001$ by the log-rank test for the between-group difference in the probability of the primary outcome.

the inflammation cascade contributes to the subsequent development of lung injury[31] and systemic organ failure.[8,32]

The use of very low levels of PEEP in previous trials may have promoted the repeated opening and closing of small airways, leading to atelectasis, which can precipitate the development of pulmonary complications.[6,33] We used a multifaceted strategy of lung-protective ventilation that combined low tidal volumes, recruitment maneuvers to open collapsed alveoli, and moderate levels of PEEP to prevent further collapse.[34] Other strengths of the present trial include the methods used to minimize bias (blinded and centralized randomization, complete follow-up, and intention-to-treat analyses); the pragmatic nature of the trial protocol, with routine practice being maintained; and the enrollment of patients with characteristics similar to those of patients enrolled in other studies analyzing outcomes after major surgery.[29]

Our findings are consistent with the observation of transient arterial hypotension during recruitment maneuvers.[35] Consequently, recruitment maneuvers, in which hemodynamic effects are potentially influenced by the applied level of alveolar pressure,[36] should be used with caution in patients with hemodynamic instability.

There are several limitations to our study. The trial design did not include standardization of the administration of fluids. However, this limitation is unlikely to have affected our results, since the volume of fluids administered was similar in the two groups. The definition of nonprotective ventilation was arbitrary but is supported in the literature.[19,20] The trial protocol did not include standardization of requirements for noninvasive ventilation; however, it was recommended that the study centers follow clinical-practice guidelines,[37,38] and postoperative care was conducted by health care workers who were unaware of the study assignments. The utilization of noninvasive ventilation in our trial is close to that reported in earlier studies.[37] We therefore consider it unlikely that any imbalance in interventions affected our results.

In conclusion, our study provides evidence that a multifaceted strategy of prophylactic lung-protective ventilation during surgery, as compared with a practice of nonprotective mechanical ventilation, results in fewer postoperative complications and reduced health care utilization.

Dr. Futier reports receiving consulting fees from General Electric Medical Systems, lecture fees from Fresenius Kabi, and reimbursement of travel expenses from Fisher and Paykel Healthcare. Dr Constantin reports receiving consulting fees from Baxter, Fresenius Kabi, Dräger, and General Electric Medical Systems, payment for expert testimony from Baxter, Dräger, and Fresenius Kabi, lecture fees from General Electric Medical Systems, Dräger, Fresenius Kabi, Baxter, Hospal, Merck Sharp & Dohme, and LFB Biomedicaments, payment for the development of educational presentations from Dräger, General Electric Medical Systems, Baxter, and Fresenius Kabi, and reimbursement of travel expenses from Bird, Astute Medical, Astellas, Fresenius Kabi, Baxter, and Hospal. Dr. Paugam-Burtz reports receiving consulting fees from Fresenius Kabi, lecture fees and reimbursement of travel expenses from Astellas, and payment for the development of educational presentations from LFB Biomedicaments and Merck Sharp & Dohme. Dr. Allaouchiche reports receiving consulting fees from Fresenius Kabi and lecture fees from Novartis and Astellas. Dr. Leone reports receiving consulting fees from LFB Biomedicaments and lecture fees from Fresenius Kabi and Novartis. Dr. Jaber reports receiving consulting fees from Dräger France and Maquet France, lecture fees from Fisher and Paykel Healthcare, Abbott, and Philips, and reimbursement of travel expenses from Pfizer. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Since publication of their article, the authors report no further potential conflict of interest.

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Intraoperative Low-Tidal-Volume Ventilation

TO THE EDITOR: We are troubled by the ventilation strategy selected for the control group (or nonprotective-ventilation group) in the study by Futier et al. (Aug. 1 issue).[1] This strategy (nonprotective ventilation with a tidal volume of 10 to 12 ml per kilogram of predicted body weight, with no positive end-expiratory pressure [PEEP] and no recruitment maneuvers) is known to be potentially harmful and is outdated (the authors cite a study from 1963[2] to define their standard of care). The tidal volumes recommended in contemporary strategies[3,4] for perioperative ventilation are less than 10 ml per kilogram of predicted body weight, and they are provided with PEEP.

To analyze practice patterns for patients undergoing anesthesia, we undertook a study in which we reviewed data from 230,386 surgical procedures at two institutions. These data show that PEEP with a median of 5 cm of water was used in 60.4% of procedures. Median tidal volumes declined from 9.2 to 7.9 ml per kilogram of predicted body weight between 2005 and 2013.

Prospective studies such as that by Futier et al. are most relevant if they derive their data from recent observational studies that used contemporary standards of care. Moreover, these data can be derived from clinical-decision support databases.[5] Do the authors have contemporary data to support their choice of ventilation strategies?

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TO THE EDITOR: Futier et al. attributed the outcome of fewer postoperative complications in the protective-ventilation group, in which low-tidal-volume ventilation and PEEP were used, mainly to the prevention of atelectasis. We postulate that microaspiration could be another reason for the higher rate of postoperative pneumonia in the nonprotective-ventilation group.

In our recent study,[1] we found that without the provision of PEEP there was downward leakage of fluid across the cuff of the endotracheal tube, even at a recommended cuff pressure of 20 to 30 cm of water. This leakage was eliminated with the use of a PEEP as low as 5 cm of water or with the use of endotracheal tubes with newer cuff designs. In another study[2] in which high-tidal-volume ventilation was compared with low-tidal-volume ventilation, with a PEEP of 5 cm of water in both groups during major upper abdominal surgery, no significant difference was detected in postoperative lung function or clini-

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cal outcome. We believe the application of PEEP is the critical variable in the study by Futier et al. We also wonder whether the inflammatory condition associated with pneumonia contributed to the anastomotic leak.

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TO THE EDITOR: Futier et al. compared two approaches to ventilation during laparoscopic and open surgery (laparotomy). Primary outcomes were recorded in 69 of the 85 patients undergoing laparoscopic surgery and in 7 of 315 patients undergoing nonlaparoscopic open surgery. The primary strategies used in open and laparoscopic surgical ventilation support are different, partly because of the insufflation of carbon dioxide that occurs during laparoscopic surgery.[1-4] To avoid hypercapnia and respiratory acidosis during laparoscopic surgery, it is common to use gradually increasing tidal volumes, ultimately leading to the use of high-volume–high-pressure mechanical ventilation during prolonged laparoscopic surgeries. Tidal volumes can be adjusted by monitoring the end-tidal carbon dioxide concentration and the acid–base status of the blood. To what extent were the ventilator settings changed during laparoscopic surgery to meet its unique needs? Can the lack of such adjustments explain the observed outcomes?

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THE AUTHORS REPLY: In response to Wanderer et al.: we fully concur that there has been a gradual decrease over time in the use of high-tidal-volume ventilation and that the ventilation strategy used in our control group may therefore not fully reflect practice in all hospitals. Nevertheless, lung protection is often incorrectly reduced to lowering tidal volume, with either very low levels of PEEP (<5 cm of water) or no PEEP. Low-tidal-volume ventilation alone is not only ineffective[1] but also may be deleterious. Contemporary data on the use of PEEP in addition to lower tidal volume are scarce. A recent analysis of an electronic database from the University of Colorado suggested that a combination of a tidal volume of more than 8 ml per kilogram of predicted body weight and a PEEP of less than 5 cm of water represented the standard of care in more than 60% of patients.[2] Data from our observational study indicate that regardless of the PEEP level used, a tidal volume in the range of our protective-ventilation strategy (6 to 8 ml of water per kilogram of predicted body weight) was used in 30.1% of patients.[3]

We fully agree with the comment by Lam et al. on the pivotal role of PEEP in addition to lower tidal volume in the protective-ventilation strategy. However, the additional contribution of recruitment maneuvers (which were a part of this strategy) should not be underestimated, since PEEP levels in the range of those used in our

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experimental conditions are not effective in reopening nonaerated lung regions.[4] Further investigation will be required to address the question of whether the inflammatory conditions associated with the development of pneumonia or the use of mechanical ventilation can explain anastomotic leak.

Mynbaev et al. ask about the possible influence of laparoscopic surgery on the occurrence of the primary outcome. Data presented for laparoscopic surgery in Table S1 of the Supplementary Appendix of our article (available at NEJM.org) were erroneously interchanged with the data for nonlaparoscopic surgery. The primary outcome measure should have been shown for 10 of the 85 patients who underwent laparoscopic surgery rather than for 69 of those 85 patients (odds ratio, 0.50; 95% confidence interval, 0.25 to 1.03; P=0.06) and for 66 of the 315 patients who underwent nonlaparoscopic surgery. We regret the error; a corrected version of the Supplementary Appendix is available at NEJM.org.

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Glucose Levels and Risk of Dementia

TO THE EDITOR: Crane and coworkers (Aug. 8 issue)[1] report on the relationship between glucose levels and the risk of dementia in participants whose mean age at baseline was 76 years. Their analysis is limited by the fact that the established and readily available confounder of renal function had not been accounted for. In the United States, 62.2% of persons 80 years of age or older have an estimated glomerular filtration rate (GFR) of less than 60 ml per minute per 1.73 m^2 of body-surface area.[2] Moderate renal impairment has been shown to be associated with an excess risk of incident dementia among persons in good-to-excellent health.[3] A community-based cross-sectional study showed that global performance and specific cognitive functions are negatively affected early in chronic kidney disease.[4] In a community-based study with a follow-up period similar to that in the study of Crane et al., the change in renal function over time was related to the change observed in global cognitive ability, verbal episodic memory, and abstract reasoning.[5] Aside from the estimated GFR, increased albuminuria is also independently associated with a faster decline in cognitive function. Hence, renal function is an important factor contributing to cognitive impairment and cognitive decline.

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THE AUTHORS REPLY: Kielstein raises the possibility that renal function may confound the association that we found between glucose levels and dementia risk. We are aware of the literature that Kielstein references. Indeed, these data pro-

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