Protective *versus* Conventional Ventilation for Surgery

A Systematic Review and Individual Patient Data Meta-analysis

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ABSTRACT

Background: Recent studies show that intraoperative mechanical ventilation using low tidal volumes (V_T) can prevent postoperative pulmonary complications (PPCs). The aim of this individual patient data meta-analysis is to evaluate the individual associations between V_T size and positive end–expiratory pressure (PEEP) level and occurrence of PPC.

Methods: Randomized controlled trials comparing protective ventilation (low V_T with or without high levels of PEEP) and conventional ventilation (high V_T with low PEEP) in patients undergoing general surgery. The primary outcome was development of PPC. Predefined prognostic factors were tested using multivariate logistic regression.

Results: Fifteen randomized controlled trials were included (2,127 patients). There were 97 cases of PPC in 1,118 patients (8.7%) assigned to protective ventilation and 148 cases in 1,009 patients (14.7%) assigned to conventional ventilation (adjusted relative risk, 0.64; 95% CI, 0.46 to 0.88; $P < 0.01$). There were 85 cases of PPC in 957 patients (8.9%) assigned to ventilation with low V_T and high PEEP levels and 63 cases in 525 patients (12%) assigned to ventilation with low V_T and low PEEP levels (adjusted relative risk, 0.93; 95% CI, 0.64 to 1.37; $P = 0.72$). A dose–response relationship was found between the appearance of PPC and V_T size ($R^2 = 0.39$) but not between the appearance of PPC and PEEP level ($R^2 = 0.08$).

Conclusions: These data support the beneficial effects of ventilation with use of low V_T in patients undergoing surgery. Further trials are necessary to define the role of intraoperative higher PEEP to prevent PPC during nonopen abdominal surgery.

(ANESTHESIOLOGY 2015; 123:66-78)

MORE than 230 million major surgical procedures are undertaken worldwide each year.[1] Postoperative complications after major surgery increase resource use and are an important cause of death.[2] Postoperative pulmonary complications (PPCs) are suggested to have a strong impact on the morbidity and mortality of patients who need major surgery.[2]

A systematic review and meta-analysis of investigations in patients receiving ventilation during general anesthesia for surgery suggests benefit from so-called protective ventilator strategies that use low tidal volumes (V_T) with or without high positive end–expiratory pressure (PEEP) levels.[3] Two randomized controlled trials of intraoperative ventilation, published after this meta-analysis, confirm benefit from the combination of low V_T and high PEEP levels.[4,5] Another

What We Already Know about This Topic

- Postoperative pulmonary complications (PPC) are suggested to have a strong impact on the morbidity and mortality of major surgical patients
- Although recent systematic review suggests benefit of intraoperative protective ventilation with low tidal volume either with or without high positive end–expiratory pressure (PEEP) for reducing the PPC, independent role of the tidal volume and PEEP is not clarified

What This Article Tells Us That Is New

- This individual patient meta-analysis of 2,127 patients ventilated under general anesthesia for surgery from 15 randomized controlled trials shows that intraoperative ventilation with low tidal volume protects against postoperative pulmonary complications (PPC), but further trials are necessary to define the role of intraoperative higher positive end–expiratory pressure to prevent PPC after major abdominal surgery

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Submitted for publication June 27, 2014. Accepted for publication January 25, 2015. From the Department of Intensive Care, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (A.S.N., S.N.T.H., J.M.B., M.W.H., E.K.W., M.J.S.); Department of Pneumology,
 Anesthesiology 2015; 123:66-78

recent trial demonstrates no benefit from high PEEP levels with the use of low V_T but shows use of high PEEP levels to be associated with the appearance of intraoperative hypotension and increased need for vasoactive drugs.[6] Contrary, a large retrospective study showed that use of low V_T during general anesthesia for surgery is associated with increased 30-day mortality, and the investigators suggest that this negative effect was due to the use of low PEEP.[7]

To gain a better understanding of the independent role of V_T and PEEP on protective mechanical ventilation during surgery, we performed a systematic review and meta-analysis of individual patient data. We aimed to investigate the individual associations between ventilation settings, including V_T size and PEEP level, and the appearance of PPCs. We hypothesize (1) intraoperative ventilation with low V_T to protect against PPCs and (2) use of high PEEP to add to the beneficial effects of intraoperative ventilation with low V_T.

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Materials and Methods

The full methodology of this meta-analysis, the predefined protocol, and the statistical analysis plan have been published previously.[8] Due to the high number of patients from randomized controlled trials, we decided to deviate from the original protocol and chose to exclude observational studies (*i.e.*, we used only individual patient data from the randomized controlled trials).

Search Strategy

We identified eligible randomized controlled trials by a blind electronic search by two authors of MEDLINE, Cumulative Index to Nursing and Allied Health Literature, Web of Science, and Cochrane Central Register of Controlled Trials up to April 2014. The sensitive search strategy combined the following Medical Subject Headings and Keywords (protective ventilation OR lower tidal volume OR low tidal volume OR positive end-expiratory pressure OR positive end expiratory pressure OR PEEP). All reviewed articles and cross-referenced studies from retrieved articles were screened for pertinent information.

Selection of Studies

Randomized controlled trials eligible for this review compared protective with conventional ventilation in adult patients undergoing general anesthesia for surgery. Protective ventilation was defined as ventilation using low V_T (defined as a $V_T \leq$ 8 ml/kg predicted body weight [PBW]) with or without high levels of PEEP (defined as PEEP $\geq$ 5 cm H_2O) and with or without recruitment maneuvers. Conventional ventilation was defined as ventilation using high V_T (> 8 ml/kg PBW) with or without low levels of PEEP (< 5 cm H_2O) and without recruitment maneuvers. The definition of protective and conventional ventilation was made based on several reports in the literature and according to the previously published protocol.[3,4,6,8]

Authors independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information from investigators as needed. Corresponding authors of retrieved trials were asked to fill a datasheet with ventilation parameters obtained hourly during the surgical procedure. Data from each trial were checked against reported results, and queries were resolved with the principal investigator. Some of the outcomes in this report may differ slightly from those in published original study reports because we standardized outcome definitions and data analyses.

To identify potential sources of bias, we examined concealment of treatment allocation, blinding of clinical outcome assessments and data analyses, the proportion of patients lost to follow-up, and early stopping prior to enrolment of the target sample. We used the Grading of Recommendations Assessment, Development and Evaluation system to rate the

overall quality of the evidence. In this system, randomized clinical trials provide high-quality evidence unless limited by important risk of bias, imprecision, inconsistency, indirectness, or high risk of publication bias.

Outcomes

The predefined primary outcome was development of PPCs during follow-up (composite of postoperative lung injury, pulmonary infection, or barotrauma, as defined by the authors in the original studies). Predefined secondary outcomes included in-hospital mortality, intensive care unit (ICU) length of stay, and hospital length of stay.

Statistical Analysis

All patients were analyzed in the study group to which they were randomized in the original study (intention-to-treat principle). We used 2-sided *t* tests to compare respiratory variables during follow-up and likelihood ratio tests to compare statistical models.

For the primary analysis of development of PPCs, we calculated relative risks (RRs) and 95% CIs using logistic regression. The initial model included age, sex, body mass index, type of surgery, American Society of Anesthesiologists score (ASA), type of ventilation, highest PEEP used during surgery, highest plateau pressure achieved during surgery, highest compliance achieved during surgery, and presence of risk factor for PPCs (defined as shock, pneumonia, blood transfusion, and/or sepsis). Variables with *P* value of less than 0.2 in the univariate analysis are included in the multivariate regression. The final model was developed by dropping each variable in turn from the model and conducting a likelihood-ratio test to compare the full and the nested models. We used a significance level of 0.05 as the cutoff to exclude a variable from the model.

To compare in-hospital time to development of PPCs and in-hospital time to death for the groups under protective or conventional ventilation, we fitted Cox regression models with the same covariables. Time-to-event was defined as time from the day of surgery to the event in days. Cox proportional-hazards regression models were used to examine simultaneous effects of multiple covariates on outcomes, censoring a patient's data at the time of death, hospital discharge, or after 30 days. In all models, the categorical outcome variables were tested for trend with the conventional ventilation group as reference. Kaplan–Meier curves were constructed, and log-rank tests were used to determine the univariate significance of the study variables.

A priori subgroup analyses were used to assess the effect of V_T in the following predefined subgroups: (1) ASA score (< 3 *vs.* ≥ 3); (2) presence of risk factors for PPCs (yes or no, defined as pneumonia, shock, transfusion, or sepsis); (3) type of ventilation (volume or pressure controlled); (4) type of surgery (cardiac, abdominal, thoracic, or orthopedic); (5) body mass index (< 17, 18 to 25, 26 to 30, 31 to 35, or > 35 kg/m^2); (6) age (< 65 or ≥ 65 yr); and (7) sex (male or female).

To assess the individual effects of PEEP on outcome, all analyses were reassessed *post hoc* in patients ventilated with low V_T (≤ 8 ml/kg PBW) and stratified between those using low (< 5 cm H_2O) and high PEEP levels (≥ 5 cm H_2O).[4] Also, Kaplan–Meier curves of patients ventilated with PEEP at least 5 cm H_2O were constructed to compare ventilation with V_T up to 7 ml/kg PBW *versus* 8 to 10 ml/kg PBW *versus* more than 10 ml/kg PBW. These cutoffs were chosen based on the cutoffs usually used in the literature for low (6 ml/kg PBW) and high V_T (10 to 12 ml/kg PBW) and the level between them.[4–7] Also, in a *post hoc* analysis, we analyzed the relationship between four cutoffs of PEEP (0 to 2, 3 to 5, 6 to 8, and ≥ 9 cm H_2O, with 0 to 2 cm H_2O as the reference) and V_T (3 to 5, 6 to 8, 9 to 11, and ≥ 12 ml/kg PBW with ≥ 12 ml/kg PBW as the reference) with the primary outcome. Finally, in a *post hoc* analysis, we analyzed recruitment maneuvers as a dichotomous variable in the regression model, using nonrecruitment as reference, and adjusted by the same set of covariables described in the second paragraph of this section.

PROBIT regression analysis was used to characterize the dose–response relationship between the intraoperative V_T size and PEEP level and the probability of PPCs, while adjusting for the same set of covariates used in the final Cox model. A quadratic term was used in the final model for PEEP and V_T. The quadratic term was chosen because we hypothesize that the relationship between PEEP, V_T, and PPC is curvilinear and the highest-degree term is the second degree. This was confirmed by the inspection of the residuals.

All analyses were conducted with SPSS v.20 (IBM SPSS Statistics for Windows, Version 20.0.; IBM Corp., USA) or R v.2.12.0 (version 2.12.0; R Foundation for Statistical Computing, Austria). For all analyses, two-sided *P* values of less than 0.05 were considered significant.

Results

Search Results and Collection of Individual Patient Data

The search identified 21 randomized controlled trials of intraoperative ventilation comparing different V_T size and PEEP levels. We were not able to collect data from six trials due to the following reasons: the corresponding author could not provide data of interest or had no longer access to the complete database (n = 3)[9–11] or the corresponding author could not be contacted (n = 3).[12–14] The total enrolment based on 15 trial trials for which individual patient data could be collected was 2,127 patients (fig. 1; table 1).[4,6,15–26] In one trial, the difference between the two groups was restricted to use of recruitment maneuvers,[25] in one trial use of recruitment maneuvers and PEEP level[6] and in three trials the V_T size.[18,22,23] In the other trials, both V_T size and PEEP level differed between the two arms of the trial. The methodological quality of included trials was high, with 13 trials using concealed randomization, six trials using blind data analysis, and only three trials having minimal lost to follow-up.

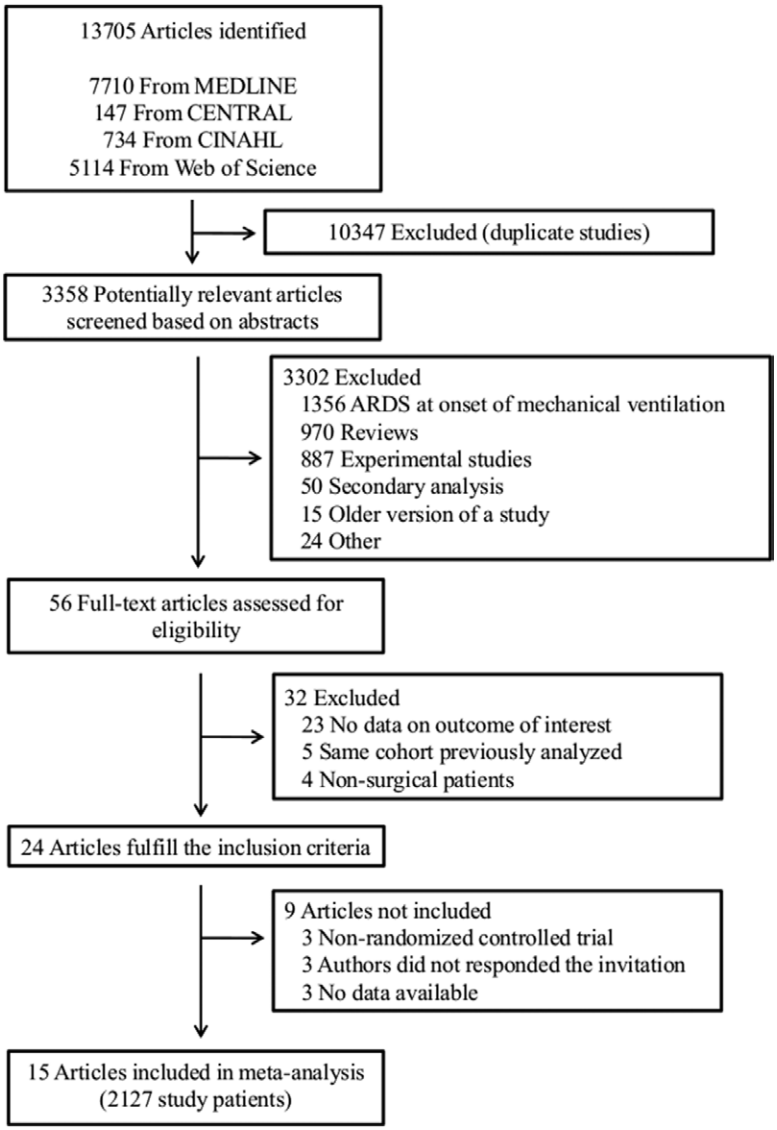

Fig. 1. Trial flow. ARDS = acute respiratory distress syndrome.

Patient Characteristics and Ventilator Settings

Patient characteristics and ventilator settings are shown in tables 2 and 3. Patients receiving protective ventilation were ventilated with higher PEEP levels, respiratory rates, plateau pressure, and higher $Paco_2$ levels during intraoperative ventilation, as compared with those receiving conventional ventilation. V_T was higher in patients who received conventional ventilation during the whole period of ventilation, as compared with patients receiving protective ventilation.

Associations between Intraoperative Ventilator Settings and the Primary and Secondary Endpoints

The appearance of PPCs was lower in patients receiving protective ventilation compared with patients receiving conventional ventilation (adjusted RR, 0.64; 95% CI, 0.46 to 0.88; $P < 0.01$) (table 4; fig. 2). In-hospital mortality and length of stay in ICU and hospital were similar between the two groups, although patients who developed a PPC had a higher ICU length of stay (6.3 *vs.* 1.1 days; $P < 0.01$), a higher hospital length of stay (20.6 *vs.* 17.1 days; $P = 0.011$), and died more frequently (6.8 *vs.* 1.5%; $P < 0.01$). There was no significant interaction for the effects of protective ventilation on primary outcome according to predefined subgroup analyses, like the ASA score ($P = 0.96$ for interaction), type of surgery ($P = 0.44$ for interaction), body mass index ($P = 0.77$ for interaction), and sex ($P = 0.85$ for interaction) (fig. 3).

Associations between PEEP Levels and the Primary and Secondary Endpoints in Patients Ventilated with Low V_T

Tables 5 and 6 present characteristics and outcome for patients ventilated with low V_T and high or low PEEP levels. The appearance of PPCs was not different for patients receiving high or low PEEP levels in these patients

Table 1. Characteristics of Included Trials

Characteristics	Trials														
	Wrigge *et al.*[15]	Zupancich *et al.*[16]	Reis Miranda *et al.*[17]	Schilling *et al.*[18]	Wolthuis *et al.*[19]	Lin *et al.*[20]	Weingarten *et al.*[21]	Sundar *et al.*[22]	Treschan *et al.*[23]	Memtsoudis *et al.*[24]	Unzueta *et al.*[25]	Sev-ergnini *et al.*[5]	Futier *et al.*[4]	Maslow *et al.*[26]	PROVE Network Investigators[6]
Type of surgery	General	Cardiac	Cardiac	Thoracic	General	Thoracic	Abdominal	Cardiac	Abdomi-nal	Spine	Thoracic	Abdomi-nal	Abdomi-nal	Thoracic	Abdominal
Number of centers	1	1	1	1	1	1	1	1	1	1	1	1	7	1	30
Country	Germany	Italy	Dutch	Germany	Dutch	China	United States	United States	Germany	United States	Spain	Italy	France	United States	Europe/ United States
Number of patients															
Protective arm	29	21	23	75	24	50	20	75	52	10	40	28	200	16	455
Conventional arm	33	12	21	35	26	52	20	74	49	14	00	27	200	16	434
Validity															
Concealed allocation	Yes	NS	Yes	Yes	Yes	NS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Follow-up, %	95.4	100	100	100	100	100	100	98.7	100	100	100	98.3	100	100	100
Blinded analysis	No	No	Yes	No	No	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Stopped early	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Tidal volume, ml/kg PBW															
Protective arm	6	8	6–8	5	6	5–6	6	6	6	6	6–8	7	6–8	5	8
Conventional arm	12–15	10–12	6–8	10	12	10	10	10	12	12	6–8	9	10–12	10	8
PEEP, cm H_2O															
Protective arm	10	10	10	0–5	10	3–5	12	Scale*	5	8	8	10	6–8	5	12
Conventional arm	0	2–3	5	0–5	0	0	0		5	0	8	0	0	0	0–2
Jadad score	3	3	4	3	3	2	3	4	4	4	3	4	4	3	4

* Scale used in the ARMA trial.[27]

NS = not specified; PBW = predicted body weight; PEEP = positive end–expiratory pressure.

Table 2. Baseline Characteristics of Included Patients

Characteristics	Protective Ventilation (n = 1,118)	Conventional Ventilation (n = 1,009)
Age, yr	63.2 ± 12.8	64.7 ± 11.9
Female, no. (%)	423 (38)	383 (38)
Body mass index, kg/m^2	25.7 ± 4.4	25.7 ± 4.4
ASA, no. (%)		
Median (IQR)	2.0 (2–3)	2.0 (2–3)
1	110 (10)	109 (11)
2	557 (50)	500 (50)
3	429 (38)	379 (37)
4	22 (2)	21 (2)
Type of surgery, no. (%)		
Cardiac	119 (11)	107 (11)
Thoracic	196 (17)	119 (12)
Abdominal	793 (71)	769 (76)
Spine	10 (1)	14 (1)
Risk factor for PPC, no. (%)*		
Yes	143 (13)	149 (15)
Pneumonia	5 (0.5)	10 (1)
Sepsis	5 (0.5)	10 (1)
Transfusion	89 (8)	89 (9)
Shock	44 (4)	40 (4)

* Individual patients could have more than one risk factor.

ASA = American Society of Anesthesiologists; IQR = interquartile range; PPC = postoperative pulmonary complications.

(adjusted RR, 0.93; 95% CI, 0.64 to 1.37; P = 0.72) (table 7; fig. 4). In-hospital mortality and length of stay in ICU and hospital were also similar between these two groups. There was no association between higher cutoffs of PEEP and the incidence of PPC compared to 0 to 2 cm H_2O of PEEP (fig. 5). There was no significant interaction for the effects of PEEP on primary outcome according to predefined subgroup analyses (fig. 6). Also, the appearance of PPCs was not different for patients receiving recruitment maneuvers (adjusted RR for the whole cohort, 0.72; 95% CI, 0.49 to 1.05; P = 0.09 and adjusted RR for patients ventilated with V_T, ≤ 8 ml/kg; PBW, 0.84; 95% CI, 0.54 to 1.29; P = 0.84).

Associations between V_T Size and the Primary and Secondary Endpoints in Patients Ventilated with High PEEP

In patients ventilated with PEEP at least 5 cm H_2O, the appearance of PPCs was lower only in patients receiving V_T up to 7 ml/kg PBW compared with patients ventilated with V_T more than 10 ml/kg PBW (adjusted RR, 0.40; 95% CI, 0.21 to 0.78; P < 0.01) (fig. 7). Compared with V_T at least 12 ml/kg PBW, patients ventilated with V_T between 6 and 8 ml/kg and 3 and 5 ml/kg PBW presented a lower incidence of PPC (fig. 8). In-hospital mortality was similar between the groups. There was no significant interaction for the effects of V_T on primary outcome according to predefined subgroup analyses (fig. 9).

Table 3. Respiratory Variables during Surgery

Variable	Beginning of Procedure			Middle of Procedure			End of Procedure		
	Protective	Conventional	*P* Value	Protective	Conventional	*P* Value	Protective	Conventional	*P* Value
Tidal volume, ml/kg PBW	7.3 ± 1.0 (1,114)	10.8 ± 1.5 (918)	< 0.01	7.8 ± 1.3 (739)	10.0 ± 1.9 (671)	< 0.01	7.1 ± 1.1 (1,015)	10.3 ± 1.2 (901)	< 0.01
Plateau pressure, cm H_2O	18.8 ± 5.9 (950)	15.9 ± 4.8 (825)	< 0.01	21.3 ± 6.0 (527)	16.5 ± 5.1 (466)	< 0.01	18.4 ± 5.4 (756)	16.8 ± 4.8 (640)	< 0.01
PEEP, cm H_2O	8.6 ± 3.4 (1,011)	1.3 ± 1.8 (911)	< 0.01	7.3 ± 5.0 (723)	1.1 ± 1.6 (620)	< 0.01	6.0 ± 4.6 (1,086)	1.1 ± 1.9 (977)	< 0.01
Respiratory rate, mpm	12.4 ± 2.8 (946)	9.9 ± 2.2 (836)	< 0.01	13.0 ± 3.5 (569)	10.3 ± 2.4 (473)	< 0.01	15.1 ± 5.6 (796)	10.3 ± 2.8 (715)	< 0.01
Pao_2/Fio_2, mmHg	404.4 ± 148.0 (321)	415.2 ± 160.3 (233)	0.41	169.1 ± 194.1 (249)	197.9 ± 223.7 (203)	0.14	330.0 ± 148.5 (371)	303.7 ± 135.9 (281)	0.02
$Paco_2$, mmHg	42.4 ± 6.0 (321)	38.5 ± 7.1 (233)	< 0.01	43.5 ± 6.8 (249)	38.7 ± 8.0 (203)	< 0.01	43.7 ± 7.9 (371)	39.1 ± 6.3 (281)	< 0.01
Arterial pH	7.39 ± 0.06 (321)	7.41 ± 0.05 (233)	< 0.01	7.34 ± 0.06 (249)	7.37 ± 0.06 (203)	< 0.01	7.33 ± 0.08 (371)	7.34 ± 0.10 (281)	0.17

mpm = movements per minute; PBW = predicted body weight; PEEP = positive end–expiratory pressure.

Table 4. Clinical Outcomes in Patients Undergoing General Anesthesia for Surgery

Outcomes	Protective Ventilation (n = 1,118)	Conventional Ventilation (n = 1,009)	Adjusted RR (95% CI)*	*P* Value
Postoperative pulmonary complications	97 (8.7)	148 (14.7)	0.64 (0.46–0.88)	< 0.01
Acute respiratory distress syndrome	20 (1.8)	51 (5.1)	0.45 (0.24–0.83)	0.01
Barotrauma	12 (1.1)	29 (2.9)	0.39 (0.17–0.92)	0.03
Suspected pulmonary infection	79 (7.1)	101 (10.0)	0.83 (0.58–1.20)	0.33
In-hospital mortality	22 (2.0)	20 (2.1)	1.17 (0.52–2.62)	0.70
Length of ICU stay, days	1 (0–2)	1 (0–2)	–0.20 (–1.41 to 1.00)†	0.73
Length of hospital stay, days	10 (7–18)	11 (7–18)	–0.61 (–2.80 to 1.57)†	0.58

* Multivariate regression with the outcome of interest as dependent variable; ventilation group, age, American Society of Anesthesiologists, and presence of risk factor as independent variables. † Coefficient from a corresponding linear regression model using the same independent variables and random effect as the above-described model.

ICU = intensive care unit; RR = relative risk.

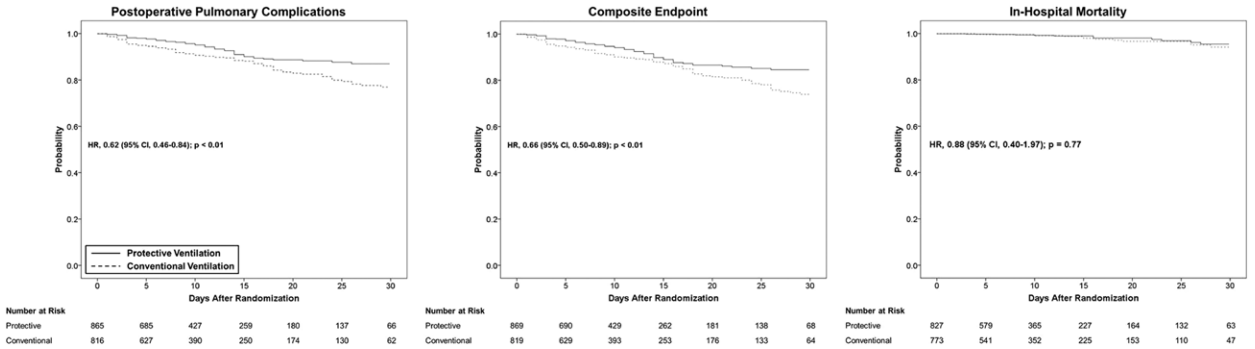

Fig. 2. Time to postoperative pulmonary complications, composite endpoint, and in-hospital mortality for protective and conventional ventilation. Cox regression models adjusted for age, American Society of Anesthesiologists, and presence of risk factor for postoperative pulmonary complications. HR = hazard ratio.

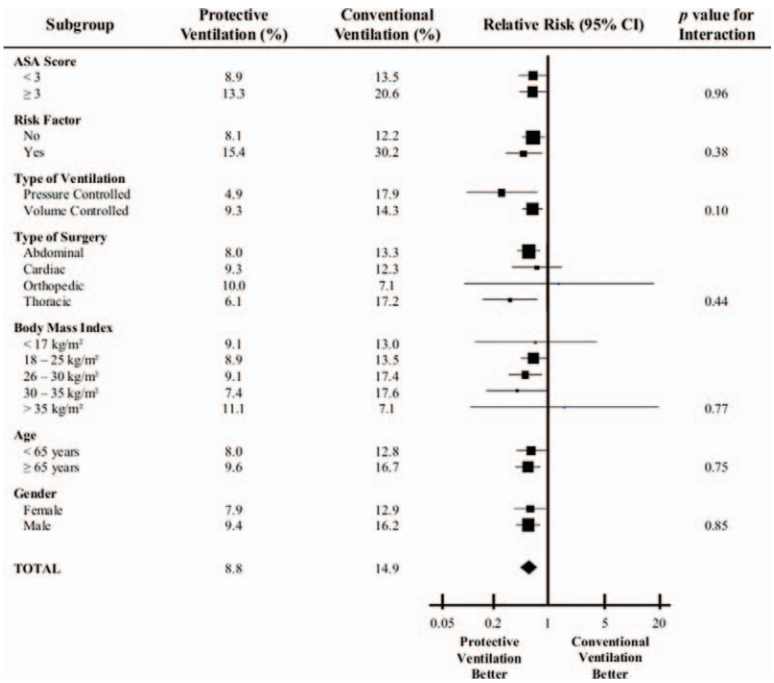

Fig. 3. Relative risk for study outcomes according to subgroups (protective *vs*. conventional ventilation). The size of the squares is proportional to the number of patients in the subgroup. ASA = American Society of Anesthesiologists.

Table 5. Baseline Characteristics of Included Patients Ventilated with Low Tidal Volumes

Characteristics	High PEEP (n = 957)	Low PEEP (n = 525)
Age, yr	63.6 ± 12.8	64.2 ± 12.8
Female, no. (%)	350 (37)	200 (38)
Body mass index, kg/m^2	25.9 ± 4.4	25.1 ± 4.3
ASA, no. (%)		
Median (IQR)	2.0 (2–3)	2.0 (2–3)
1	86 (9)	63 (12)
2	488 (51)	241 (46)
3	344 (36)	205 (39)
4	29 (3)	16 (3)
Type of surgery, no. (%)		
Cardiac	139 (14)	77 (15)
Thoracic	70 (8)	53 (10)
Abdominal	738 (77)	395 (75)
Spine	10 (1)	0 (0)
Risk factor for PPC, no. (%)*		
Yes	124 (13)	37 (7)
Pneumonia	10 (1)	10 (2)
Sepsis	5 (0.5)	3 (0.5)
Transfusion	71 (7)	19 (4)
Shock	38 (4)	5 (1)

* Individual patients could have more than one risk factor.

ASA = American Society of Anesthesiologists; IQR = interquartile range; PEEP = positive end–expiratory pressure; PPC = postoperative pulmonary complication.

Dose–Response Relationship between PEEP Level and V_T Size and PPCs

Dose–response relationship curves between intraoperative V_T size and PEEP levels and appearance of PPCs are shown in figure 10. A dose–response relationship was found between the appearance of PPC and V_T size (R^2 for mean quadratic term = 0.39) but not between the appearance of PPC and PEEP level (R^2 = 0.08).

Discussion

This individual patient meta-analysis of 2,127 patients ventilated under general anesthesia for surgery from 15 randomized controlled trials shows that intraoperative protective ventilation protects the lung from PPCs. We found that intraoperative low V_T was associated with reduced PPC.

In the ICU, following the publication of Acute Respiratory Distress Syndrome Network low V_T trial in patients with the acute respiratory distress syndrome (ARDS),[27] there has been a progressive decrease in V_T size over the last decade from more than 12 ml/kg to less than 9 ml/kg.[28–30] These changes were supported by numerous preclinical studies in animals showing that ventilation with high V_T was associated with lung inflammation and injury,[31] worse oxygenation,[32] and vascular dysfunction,[33] even in healthy lungs. In the operating room, V_T size remained unchanged, despite numerous randomized controlled trials suggesting benefit of low V_T during intraoperative ventilation.[34,35]

Table 6. Respiratory Variables during Surgery in Patients Ventilated with Low Tidal Volumes

	Beginning of Procedure			Middle of Procedure			End of Procedure		
Variable	High PEEP	Low PEEP	*P* Value*	High PEEP	Low PEEP	*P* Value*	High PEEP	Low PEEP	*P* Value*
Tidal volume, ml/kg PBW	7.5 ± 1.0 (827)	7.8 ± 0.8 (484)	0.12	7.8 ± 0.9 (406)	7.8 ± 0.9 (376)	0.95	6.7 ± 0.9 (526)	6.9 ± 1.0 (345)	0.11
Plateau pressure, cm H_2O	19.0 ± 5.7 (816)	16.0 ± 4.5 (462)	< 0.01	21.1 ± 6.0 (426)	17.3 ± 5.5 (358)	< 0.01	18.4 ± 5.5 (637)	16.7 ± 4.3 (329)	< 0.01
PEEP, cm H_2O	8.8 ± 3.3 (904)	1.2 ± 1.2 (462)	< 0.01	7.7 ± 5.0 (626)	1.1 ± 1.3 (455)	< 0.01	6.6 ± 4.5 (945)	1.0 ± 1.4 (525)	< 0.01
Respiratory rate, bpm	12.4 ± 2.8 (811)	11.4 ± 2.1 (460)	< 0.01	12.9 ± 3.6 (468)	11.8 ± 2.5 (359)	< 0.01	15.6 ± 5.9 (681)	12.0 ± 2.9 (339)	< 0.01
Pao_2/Fio_2, mmHg	422.8 ± 145.7 (249)	342.8 ± 140.5 (73)	< 0.01	174.2 ± 220.2 (180)	148.8 ± 103.0 (76)	0.33	319.3 ± 164.6 (278)	360.7 ± 127.9 (134)	0.01
$Paco_2$, mmHg	42.2 ± 5.8 (249)	43.5 ± 6.9 (73)	0.10	44.0 ± 7.1 (180)	42.6 ± 6.5 (76)	0.17	43.7 ± 8.3 (278)	43.0 ± 6.0 (134)	0.38
Arterial pH	7.39 ± 0.06 (249)	7.39 ± 0.07 (73)	0.79	7.34 ± 0.06 (180)	7.34 ± 0.06 (76)	0.86	7.34 ± 0.06 (278)	7.33 ± 0.10 (134)	0.19

* Higher PEEP *vs.* lower PEEP.

bpm = breaths/min; PBW = predicted body weight; PEEP = positive end–expiratory pressure.

Table 7. Clinical Outcomes in Patients Undergoing General Anesthesia for Surgery Ventilated with Lower Tidal Volumes

Outcomes	High PEEP (n = 957)	Low PEEP (n = 525)	Adjusted RR (95% CI)*	*P* Value
Postoperative pulmonary complications	85 (8.9)	63 (12)	0.93 (0.64–1.37)	0.72
Acute respiratory distress syndrome	20 (2.1)	15 (2.8)	0.82 (0.38–1.74)	0.60
Barotrauma	12 (1.3)	9 (1.8)	0.66 (0.25–1.77)	0.41
Suspected pulmonary infection	66 (6.9)	55 (10.4)	0.81 (0.54–1.23)	0.33
In-hospital mortality	18 (1.9)	7 (1.3)	1.34 (0.47–3.78)	0.57
Length of ICU stay, days	0 (0–1)	1 (1–2)	–0.31 (–1.91 to 1.27)†	0.69
Length of hospital stay, days	10 (7–18)	11 (8–18)	–0.48 (–3.04 to 2.07)†	0.71

* Multivariate regression with the outcome of interest as dependent variable; ventilation group, age, American Society of Anesthesiologists, and presence of risk factor as independent variables. † Coefficient from a corresponding linear regression model using the same independent variables and random effect as the above-described model.

ICU = intensive care unit; PEEP = positive end-expiratory pressure; RR = relative risk.

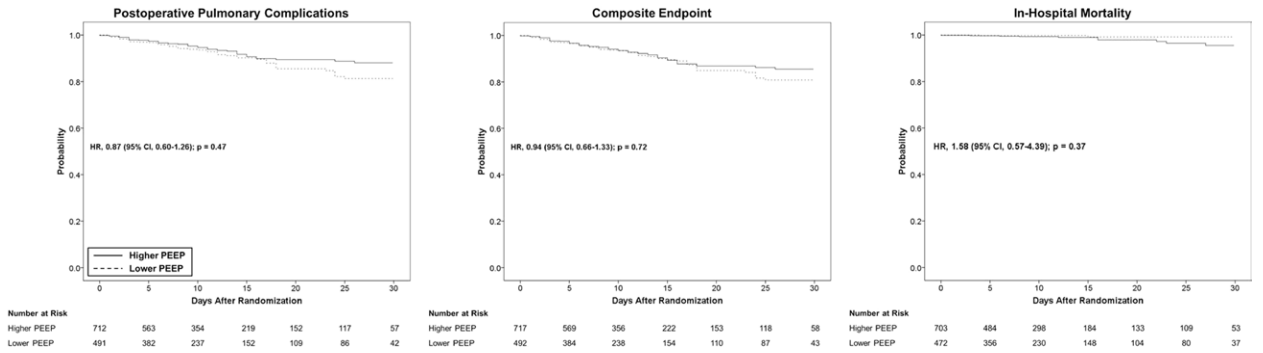

Fig. 4. Time to postoperative pulmonary complications, composite endpoint, and in-hospital mortality for patients ventilated with low tidal volumes and high or low levels of positive end–expiratory pressure (PEEP). Cox regression models adjusted for age, American Society of Anesthesiologists, and presence of risk factor for postoperative pulmonary complications. HR = hazard ratio.

Lack of knowledge of the existence and underrecognition of PPCs, as well as the idea that shorter duration of intraoperative ventilation may be less injurious than longer duration of ventilation in the ICU, may explain the absence of ventilation practice changes in the operating room.[2–4] The present analysis is in accordance with the findings of a previous systematic review and meta-analysis,[3] and three randomized controlled trials showing the benefits of protective ventilation during general anesthesia for surgery.[4–6] This meta-analysis helps further in the interpretation and understanding of the individual effects of V_T and PEEP.

Experimental studies suggest that high PEEP levels minimize cyclical alveolar collapse and corresponding shear injury to the lungs in patients with ARDS.[36,37] Based on this observation, it has been suggested that high PEEP levels could benefit patients with ARDS.[38] Randomized controlled trials comparing high PEEP levels with low PEEP levels and one meta-analysis, however, suggest only benefit of high PEEP levels in patients who suffered from severe ARDS.[38] Ventilation strategies that use high PEEP levels are associated with potentially dangerous side effects, including hemodynamic depression and lung overdistention, which could further outweigh the potential benefits.[39,40] This was also found in the last randomized controlled trial comparing high with low PEEP levels in patients under intraoperative ventilation with low V_T.[6] The results of this meta-analysis suggest no benefit from high PEEP levels with use of low V_T. Thus, high PEEP should not be standard practice, despite the suggestions of an earlier observational study.[7]

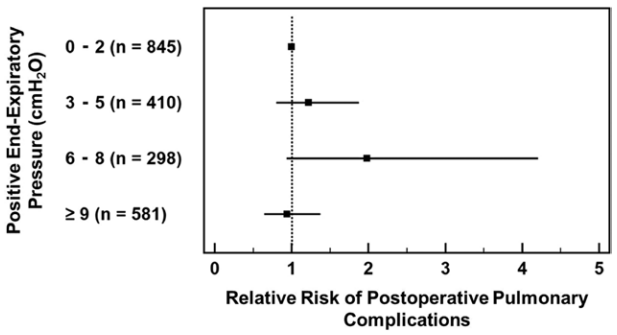

Fig. 5. Relative risk of postoperative pulmonary complications according to different levels of positive end–expiratory pressure and using 0 to 2 cm H_2O as reference.

Recently, a large and well-powered randomized controlled trial in France[4] confirmed the beneficial effects of protective ventilation in intermediate-risk and high-risk patients undergoing major surgery. However, protection in

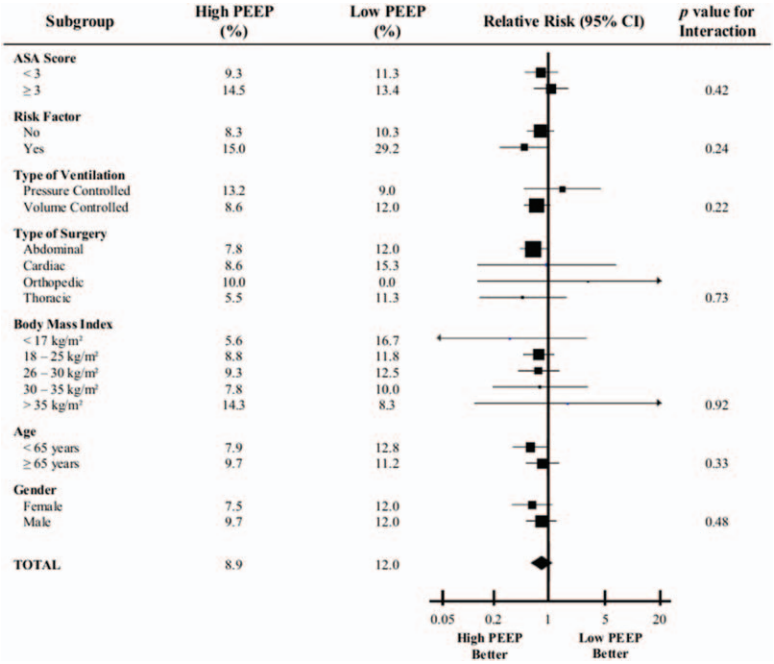

Fig. 6. Relative risk for study outcomes according to subgroups (high *vs*. low positive end–expiratory pressure [PEEP]). The size of the squares is proportional to the number of patients in the subgroup. ASA = American Society of Anesthesiologists.

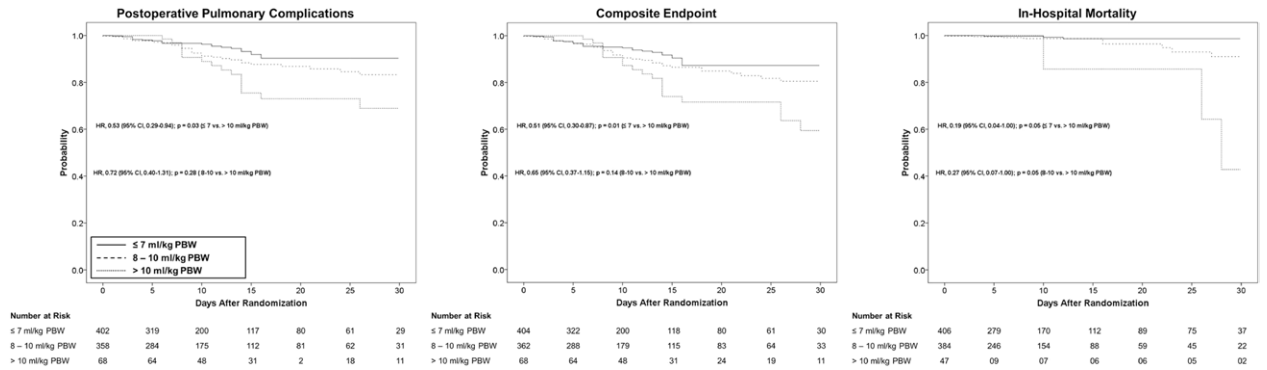

Fig. 7. Time to postoperative pulmonary complications, composite endpoint, and in-hospital mortality for patients ventilated with positive end–expiratory pressure at least 5 cm H_2O and tidal volume up to 7 ml/kg *vs*. 8 to 10 ml/kg *vs*. more than 10 ml/kg predicted body weight (PBW). Cox regression models adjusted for age, American Society of Anesthesiologists, and presence of risk factor for postoperative pulmonary complications. HR = hazard ratio.

this trial could have come from low V_T, intermediate levels of PEEP, recruitment maneuvers, or combination of the three. Indeed, the use of high V_T in the conventional arm could be associated with more harm than beneficial of low V_T in protective arm. In an attempt to understand the individual effect of PEEP, an international randomized controlled trial evaluated the effects of high PEEP levels with use of low V_T.[6] High PEEP levels did not prevent PPCs but were associated with more hemodynamic compromise.[6]

The absence of an association between a protective ventilation strategy and a lower mortality rate could be expected, since mortality of surgical patients is very low in general, and only 1.2% in the cohort of patients included in the present analysis. However, although we did no found differences in mortality and hospital length of stay in the different

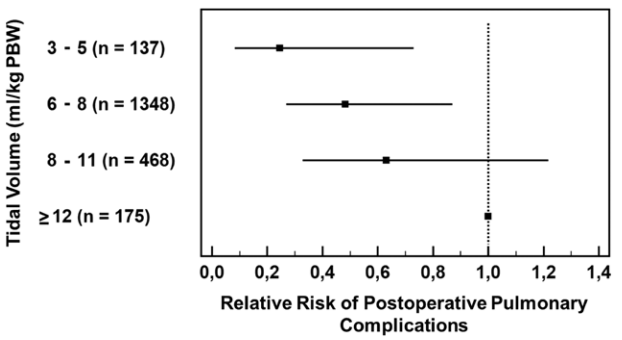

Fig. 8. Relative risk of postoperative pulmonary complications according to different tidal volumes and using at least 12 ml/kg predicted body weight (PBW) of tidal volume as reference.

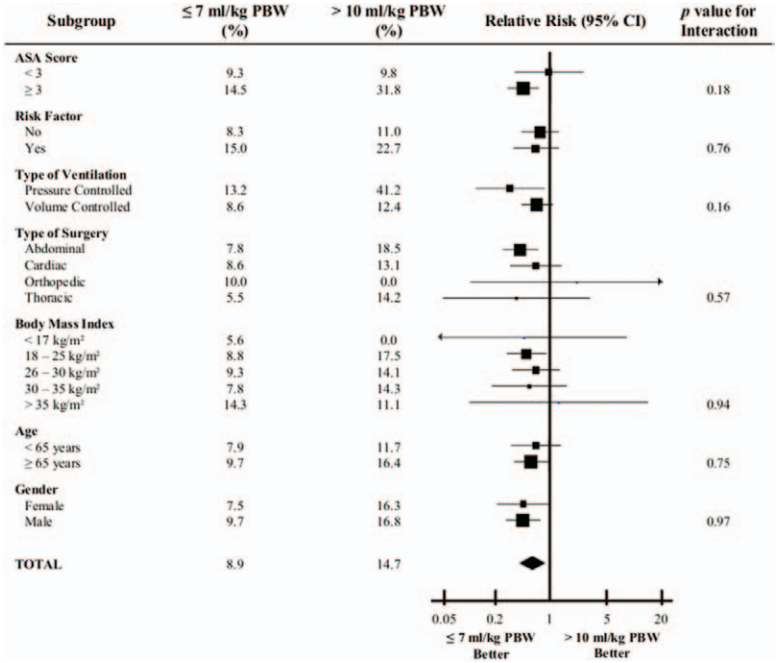

Fig. 9. Relative risk for study outcomes according to subgroups (≤ 7 ml/kg predicted body weight [PBW] *vs*. > 10 ml/kg PBW). The size of the squares is proportional to the number of patients in the subgroup. ASA = American Society of Anesthesiologists.

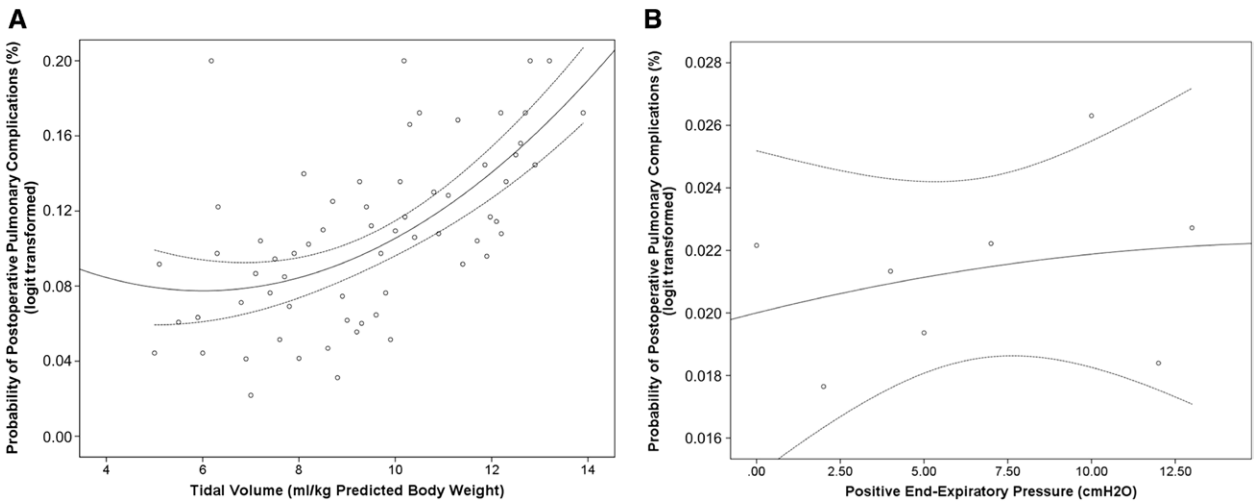

Fig. 10. PROBIT logistic regression showing the dose–response relationship curve between the mean tidal volume (ml/kg predicted body weight) (*A*) and mean positive end–expiratory pressure (PEEP) (cm H_2O) (*B*) used in surgery and the probability of postoperative pulmonary complications. *Solid line* = mean quadratic term; *dashed line* = 95% CI. The line represents the quadratic term fitting all the points. The *flat line* in the PEEP graph suggests that there is neither a positive nor a negative association between a higher level of PEEP and the development of postoperative pulmonary complications.

ventilation groups, patients who developed a PPC had a higher ICU length of stay, a higher hospital length of stay, and died more frequently.

In this meta-analysis, variability in treatment over time was overcome by conducting a pooled analysis of data on individual patients. The use of these data allowed us to update the number of patients and follow-up after the original published reports. With individual patient data, we have enough power to study different subgroups and also to assess the individual effects of PEEP and V_T. Also, to date, this study included data on the largest population available for comparison of the benefits of protective ventilation in the surgical setting and postoperative outcome.[41]

This meta-analysis knows limitations. First, not all investigators could provide the data, and therefore, data from six identified studies were not included.[9–14] However, the results of a classical meta-analysis including all but one study[14] are in agreement with those found in the present analysis. Thus, the assumption can be made that the included studies are reliable representatives of all studies of protective ventilation

during surgery.[5] Second, since the diagnosis of postoperative lung injury is based on clinical criteria, misclassification of patients might underestimate the observed effect, but this factor should have equally affect the different groups analyzed. Third, we do not have information on some important factors that could contribute to the development of postoperative complications, including but not limited to fluid balance, use of colloids, recruitment maneuvers, and postoperative analgesia. Fourth, since we collected sufficient data on other PPCs, we deviate from the primary outcome stated in the preliminary protocol (development of ARDS)[8] to a stronger outcome (development of any PPC), as PPCs were reported in the majority of retrieved studies. Fifth, different types of surgery were analyzed and can be a confounding factor. However, no interaction was found between type of surgery and primary outcome according to the predefined subgroup analyses. Finally, due to the variability between the effects on primary outcome, our analysis on PEEP could be underpowered. In fact, the highest PEEP quartile was lower than 1 compared with 0 to 2 cm H_2O PEEP. However, the moderate PEEP group 6 to 8 cm H_2O showed a nonsignificant increase, and not decrease, in the risk of PPC. Higher PEEP was found not effective to reduce PPC when protective V_T were used during open abdominal surgery.[6] Also, most of the studies included in the analysis were not *a priori* conducted to evaluate PEEP effects. Additional studies are required to test the hypothesis that high levels of PEEP during different type of surgery can protect our patients from postoperative respiratory complications.

In conclusion, this individual patient data meta-analysis shows that intraoperative ventilation with low V_T protects against PPCs. Further trials are necessary to define the role of intraoperative higher PEEP to prevent PPC during nonopen abdominal surgery.

Acknowledgments

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

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