

# Protective versus Conventional Ventilation for Surgery

## A Systematic Review and Individual Patient Data Meta-analysis

Ary Serpa Neto, M.D., M.Sc., Ph.D., Sabine N. T. Hemmes, M.D., Carmen S. V. Barbas, M.D., Ph.D., Martin Beiderlinden, M.D., Michelle Biehl, M.D., Jan M. Binnekade, Ph.D., Jaime Canet, M.D., Ph.D., Ana Fernandez-Bustamante, M.D., Ph.D., Emmanuel Futier, M.D., Ph.D., Ognjen Gajic, M.D., Ph.D., Göran Hedenstierna, M.D., Ph.D., Markus W. Hollmann, M.D., Ph.D., Samir Jaber, M.D., Ph.D., Alf Kozian, M.D., Ph.D., Marc Licker, M.D., Wen-Qian Lin, M.D., Andrew D. Maslow, M.D., Stavros G. Memtsoudis, M.D., Ph.D., Dinis Reis Miranda, M.D., Pierre Moine, M.D., Thomas Ng, M.D., Domenico Paparella, M.D., Christian Putensen, M.D., Ph.D., Marco Ranieri, M.D., Ph.D., Federica Scavonetto, M.D., Thomas Schilling, M.D., Ph.D., D.E.A.A., Werner Schmid, M.D., Ph.D., Gabriele Selmo, M.D., Paolo Severgnini, M.D., Juraj Sprung, M.D., Ph.D., Sugantha Sundar, M.D., Daniel Talmor, M.D., M.P.H., Tanja Treschan, M.D., Carmen Unzueta, M.D., Ph.D., Toby N. Weingarten, M.D., Esther K. Wolthuis, M.D., Ph.D., Hermann Wrigge, M.D., Ph.D., Marcelo Gama de Abreu, M.D., Ph.D., Paolo Pelosi, M.D., F.E.R.S., Marcus J. Schultz, M.D., Ph.D.; for the PROVE Network Investigators



This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

### 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)

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

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.<sup>3</sup> 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.<sup>4,5</sup> 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

Corresponding article on page 12.

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, Copyright © 2015, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. 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.<sup>6</sup> 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.<sup>7</sup>

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  $V_T$ .

## Materials and Methods

The full methodology of this meta-analysis, the predefined protocol, and the statistical analysis plan have been published previously.<sup>8</sup> 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<sub>2</sub>O) 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<sub>2</sub>O) 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.<sup>3,4,6,8</sup>

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

Heart Institute (INCOR), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil (A.S.N., C.S.V.B.); Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil (A.S.N., C.S.V.B.); Department of Anaesthesiology, Düsseldorf University Hospital, Düsseldorf, Germany (M. Beiderlinden, T.T.); Department of Anaesthesiology, Marienhospital Osnabrück, Osnabrück, Germany (M. Beiderlinden); Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota (M. Biehl, O.G., J.S.); Department of Anesthesiology, Hospital Universitar I Germans Trias I Pujol, Barcelona, Spain (J.C.); Department of Anesthesiology, University of Colorado, Aurora, Colorado (A.F.-B., P.M.); Department of Anesthesiology and Critical Care Medicine, Estaing University Hospital, Clermont-Ferrand, France (E.F.); Department of Medical Sciences, Section of Clinical Physiology, University Hospital, Uppsala, Sweden (G.H.); Department of Critical Care Medicine and Anesthesiology (SAR B), Saint Eloi University Hospital, Montpellier, France (S.J.); Department of Anesthesiology and Intensive Care Medicine, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany (A.K., T.S.); Department of Anaesthesiology, Pharmacology and Intensive Care, Faculty of Medicine, University Hospital of Geneva, Geneva, Switzerland (M.L.); State Key Laboratory of Oncology of South China, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, People's Republic of China (W.-Q.L.); Department of Anesthesiology, The Warren Alpert School of Brown University, Providence, Rhode Island (A.D.M.); Department of Anesthesiology, Hospital for Special Surgery, Weill Medical College of Cornell University, New York, New York (S.G.M.); Department of Intensive Care, Erasmus MC, Rotterdam, The Netherlands (D.R.M.); Department of Surgery, The Warren Alpert School of Brown University, Providence, Rhode Island (T.N.); Division of Cardiac Surgery, Department of Emergency and Organ Transplant, University of Bari Aldo Moro, Bari, Italy (D.P.); Department of Anesthesiology, University of Bonn, Bonn, Germany (C.P.); Anestesiologia e Rianimazione, Dipartimento di Discipline Medico-Chirurgiche, Università di Torino, Turin, Italy (M.R.); Department of Anesthesiology and Anesthesia Clinical Research Unit, Mayo Clinic College of Medicine, Mayo Clinic, Rochester, Minnesota (F.S., T.N.W.); Department of Cardiothoracic and Vascular Anesthesia and Intensive Care, Medical University, Vienna, Austria (W.S.); Department of Environment, Health and Safety, University of Insubria, Varese, Italy (G.S., P.S.); Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts (S.S., D.T.); Department of Anaesthesiology, Hospital de Sant Pau, Barcelona, Spain (C.U.); Department Anesthesiology and Intensive Care Medicine, University of Leipzig, Leipzig, Germany (H.W.); Department of Anesthesiology and Intensive Care Medicine, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany (M.G.d.A.); Department of Surgical Sciences and Integrated Diagnostics, IRCCS San Martino IST, University of Genoa, Genoa, Italy (P.P.); and Laboratory of Experimental Intensive Care and Anesthesiology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (M.J.S.).

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.  $\geq 3$ ); (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<sup>2</sup>); (6) age ( $< 65$  or  $\geq 65$  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  $V_T$  ( $\leq 8$  ml/kg PBW) and stratified between those using low ( $< 5$  cm H<sub>2</sub>O) and high PEEP levels ( $\geq 5$  cm H<sub>2</sub>O).<sup>4</sup> Also, Kaplan–Meier curves of patients ventilated with PEEP at least 5 cm H<sub>2</sub>O 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.<sup>4–7</sup> 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  $\geq 9$  cm H<sub>2</sub>O, with 0 to 2 cm H<sub>2</sub>O as the reference) and  $V_T$  (3 to 5, 6 to 8, 9 to 11, and  $\geq 12$  ml/kg PBW with  $\geq 12$  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.

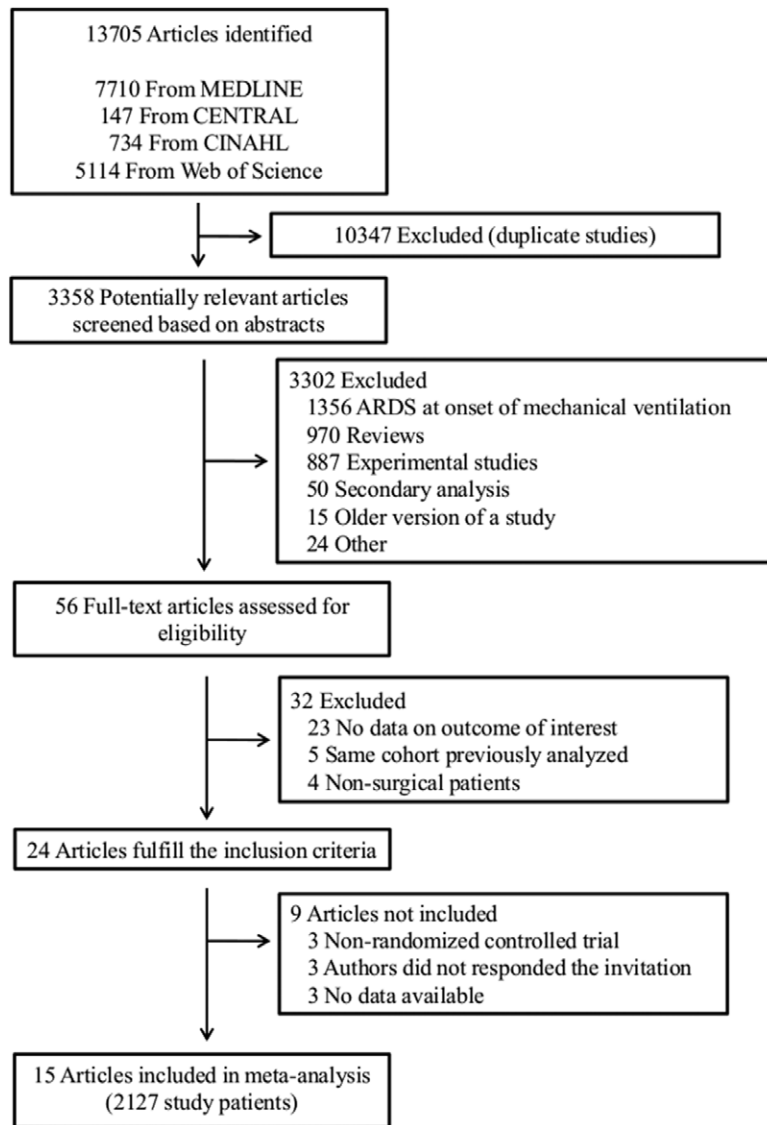
PROBIT regression analysis was used to characterize the dose–response relationship between the intraoperative  $V_T$  size and PEEP level and the probability of PPCs, while adjusting for the same set of covariates used in the final Cox model. A quadratic term was used in the final model for PEEP and  $V_T$ . 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 ( $n = 3$ )<sup>9–11</sup> or the corresponding author could not be contacted ( $n = 3$ ).<sup>12–14</sup> The total enrolment based on 15 trial trials for which individual patient data could be collected was 2,127 patients (fig. 1; table 1).<sup>4,6,15–26</sup> In one trial, the difference between the two groups was restricted to use of recruitment maneuvers,<sup>25</sup> in one trial use of recruitment maneuvers and PEEP level<sup>6</sup> and in three trials the  $V_T$  size.<sup>18,22,23</sup> 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  $P_{aCO_2}$  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. <sup>15</sup>	Zupancich et al. <sup>16</sup>	Miranda et al. <sup>17</sup>	Schilling et al. <sup>18</sup>	Wolthuis et al. <sup>19</sup>	Lin et al. <sup>20</sup>	Weingarten et al. <sup>21</sup>	Sundar et al. <sup>22</sup>	Treschan et al. <sup>23</sup>	Memtsoudis et al. <sup>24</sup>	Unzueta et al. <sup>25</sup>	Severgnini et al. <sup>5</sup>	Futier et al. <sup>4</sup>	Maslow et al. <sup>26</sup>	PROVE Network Investigators <sup>6</sup>
Type of surgery	General	Cardiac	Cardiac	Thoracic	General	Thoracic	Abdominal	Cardiac	Abdominal	Spine	Thoracic	Abdominal	Abdominal	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 <sub>2</sub> O															
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	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.<sup>27</sup>

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 <sup>2</sup>	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<sub>2</sub>O 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*<sub>T</sub> ≤ 8 ml/kg; PBW, 0.84; 95% CI, 0.54 to 1.29; *P* = 0.84).

**Associations between *V*<sub>T</sub> Size and the Primary and Secondary Endpoints in Patients Ventilated with High PEEP**

In patients ventilated with PEEP at least 5 cm H<sub>2</sub>O, the appearance of PPCs was lower only in patients receiving *V*<sub>T</sub> up to 7 ml/kg PBW compared with patients ventilated with *V*<sub>T</sub> 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*<sub>T</sub> at least 12 ml/kg PBW, patients ventilated with *V*<sub>T</sub> 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*<sub>T</sub> 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	<i>P</i> Value	Protective	Conventional	<i>P</i> Value	Protective	Conventional	<i>P</i> 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 <sub>2</sub> O	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 <sub>2</sub> O	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
Pac <sub>2</sub> /Fio <sub>2</sub> , 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 <sub>2</sub> , 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

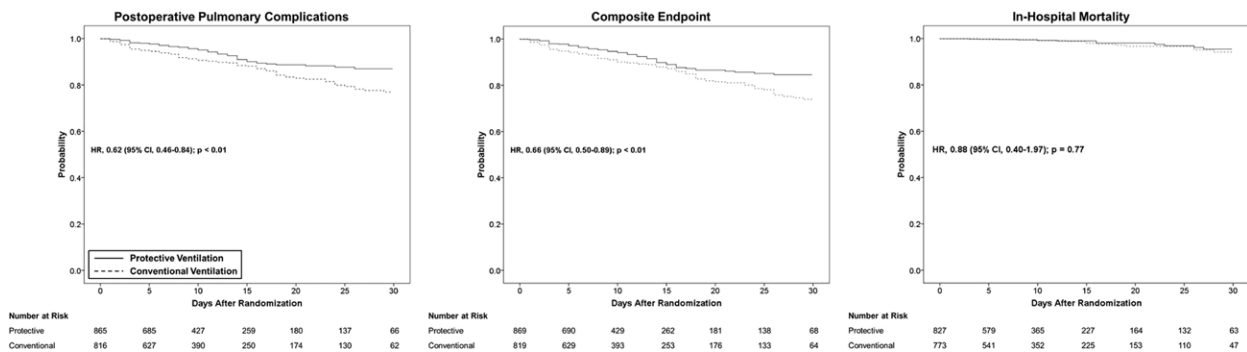
mpm = movements per minute; PBW = predicted body weight; PEEP = positive end-expiratory pressure.

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

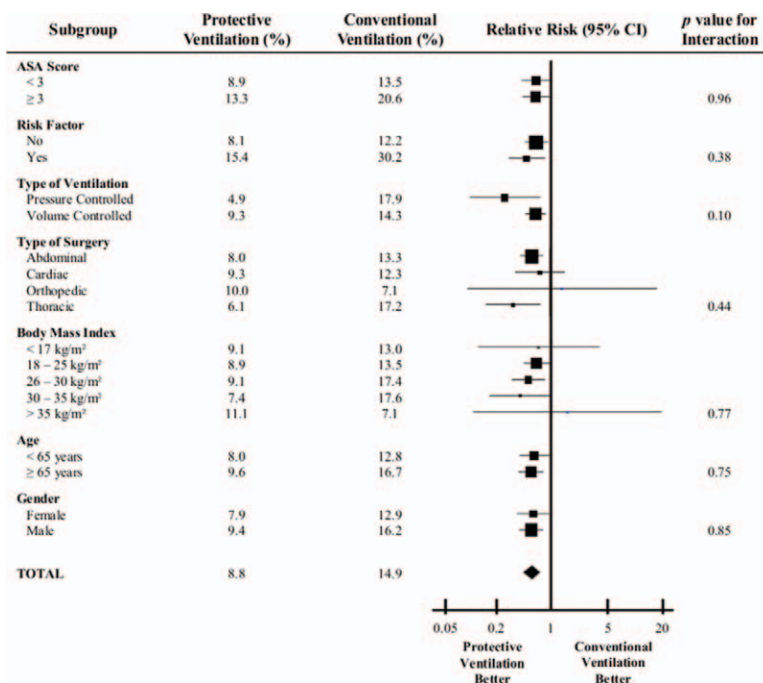
Outcomes	Protective Ventilation (n = 1,118)	Conventional Ventilation (n = 1,009)	Adjusted RR (95% CI)*	P Value
Postoperative pulmonary complications	97 (8.7)	148 (14.7)	0.64 (0.46–0.88)	< 0.01
Acute respiratory distress syndrome	20 (1.8)	51 (5.1)	0.45 (0.24–0.83)	0.01
Barotrauma	12 (1.1)	29 (2.9)	0.39 (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 <sup>2</sup>	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<sub>T</sub> Size and PPCs**

Dose–response relationship curves between intraoperative V<sub>T</sub> 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<sub>T</sub> size (R<sup>2</sup> for mean quadratic term = 0.39) but not between the appearance of PPC and PEEP level (R<sup>2</sup> = 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<sub>T</sub> was associated with reduced PPC.

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

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

Variable	Beginning of Procedure			Middle of Procedure			End of Procedure		
	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 <sub>2</sub> O	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 <sub>2</sub> O	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 <sub>2</sub> /Fio <sub>2</sub> , 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 <sub>2</sub> , 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.

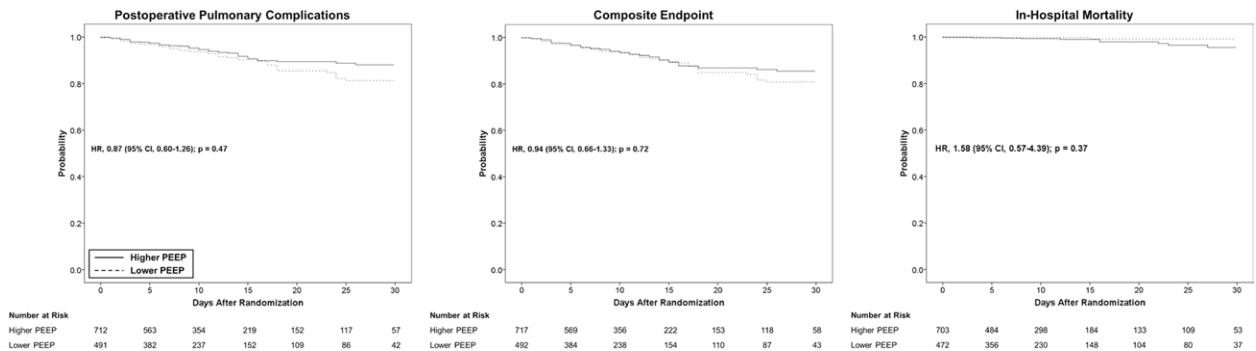


**Table 7.** Clinical Outcomes in Patients Undergoing General Anesthesia for Surgery Ventilated with Lower Tidal Volumes

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.

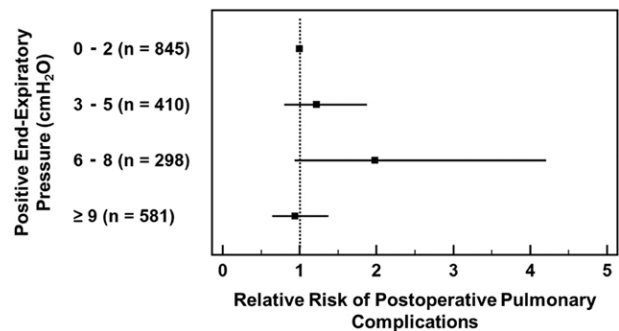
ICU = intensive care unit; PEEP = positive end-expiratory pressure; RR = relative risk.



**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.<sup>2–4</sup> The present analysis is in accordance with the findings of a previous systematic review and meta-analysis,<sup>3</sup> and three randomized controlled trials showing the benefits of protective ventilation during general anesthesia for surgery.<sup>4–6</sup> 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.<sup>36,37</sup> Based on this observation, it has been suggested that high PEEP levels could benefit patients with ARDS.<sup>38</sup> 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.<sup>38</sup> 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.<sup>39,40</sup> This was also found in the last randomized controlled trial comparing high with



**Fig. 5.** Relative risk of postoperative pulmonary complications according to different levels of positive end-expiratory pressure and using 0 to 2 cm H<sub>2</sub>O as reference.

low PEEP levels in patients under intraoperative ventilation with low  $V_T$ .<sup>6</sup> 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.<sup>7</sup>

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

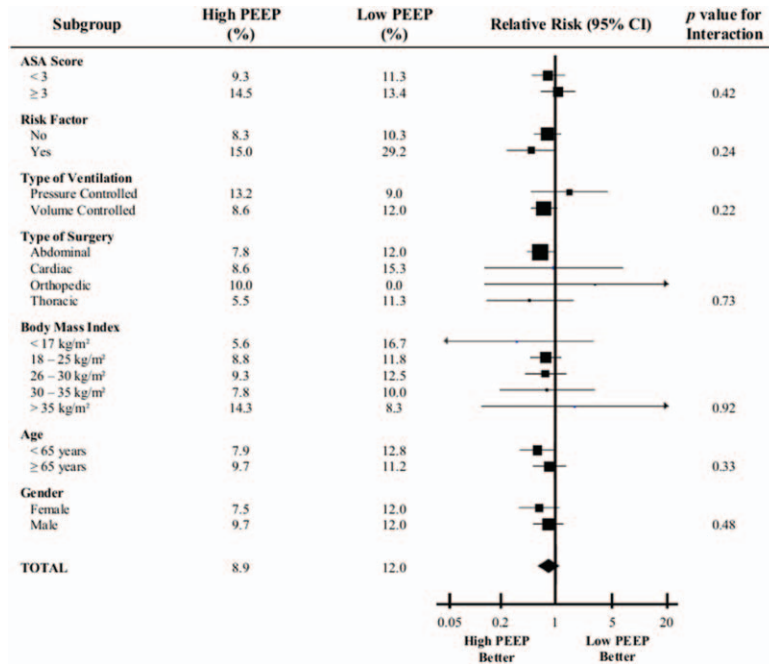


Fig. 6. Relative risk for study outcomes according to subgroups (high vs. low positive end-expiratory pressure [PEEP]). The size of the squares is proportional to the number of patients in the subgroup. ASA = American Society of Anesthesiologists.

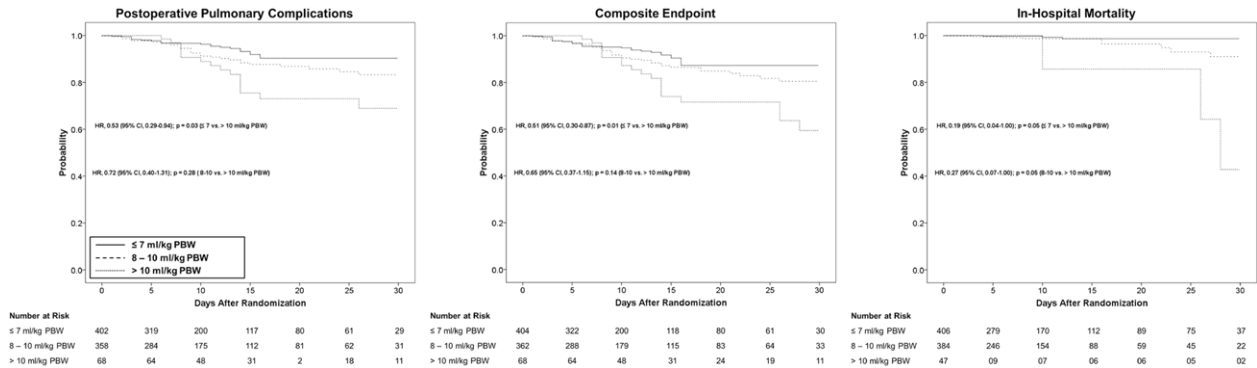


Fig. 7. Time to postoperative pulmonary complications, composite endpoint, and in-hospital mortality for patients ventilated with positive end-expiratory pressure at least 5 cm H<sub>2</sub>O and tidal volume up to 7 ml/kg vs. 8 to 10 ml/kg vs. more than 10 ml/kg predicted body weight (PBW). Cox regression 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  $V_T$ .<sup>6</sup> High PEEP levels did not prevent PPCs but were associated with more hemodynamic compromise.<sup>6</sup>

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 not find differences in mortality and hospital length of stay in the different

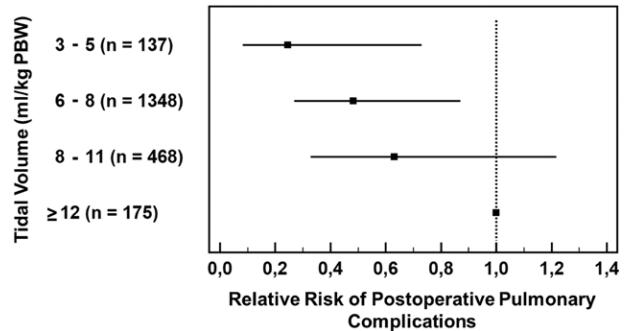
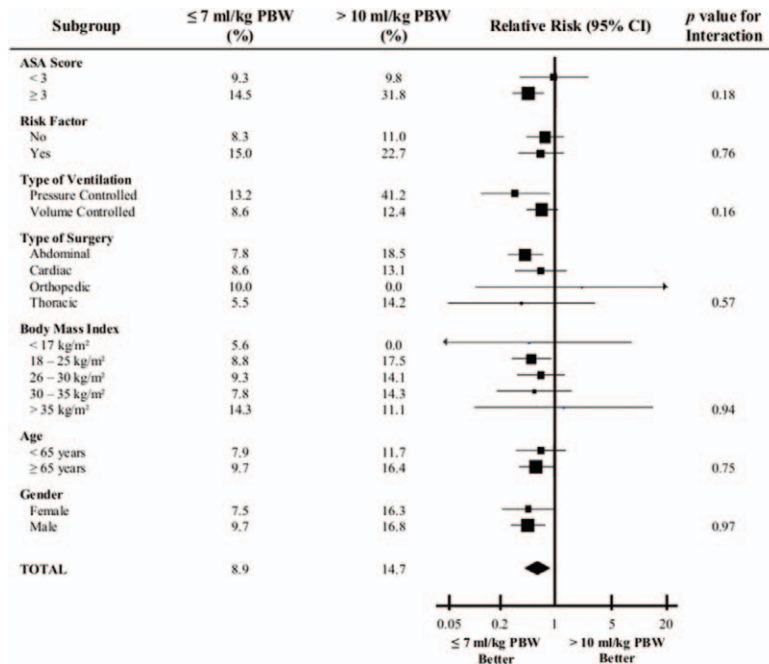
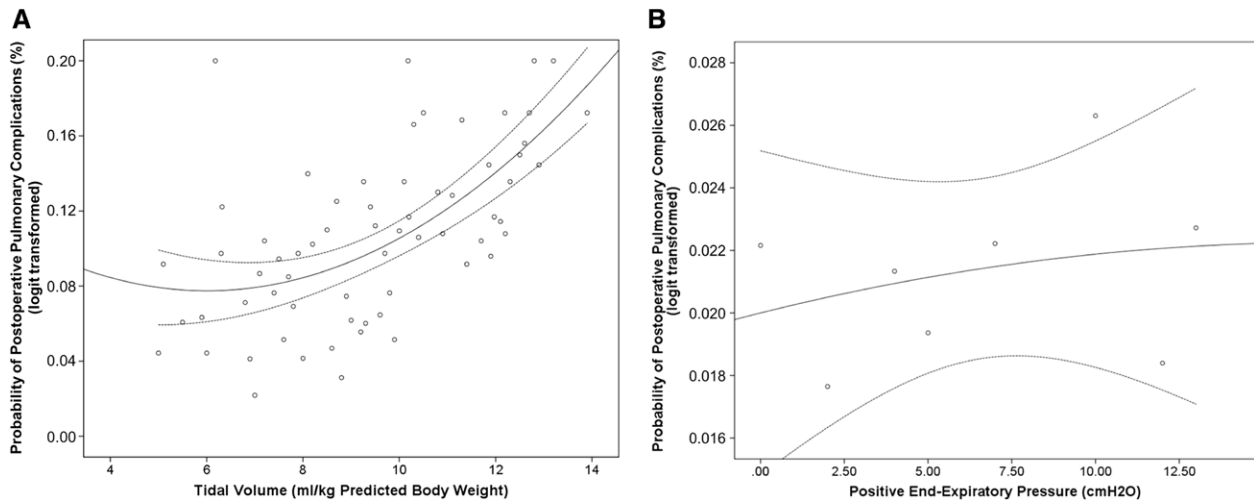


Fig. 8. Relative risk of postoperative pulmonary complications according to different tidal volumes and using at least 12 ml/kg predicted body weight (PBW) of tidal volume as reference.



**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<sub>2</sub>O) (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.<sup>41</sup>

This meta-analysis knows limitations. First, not all investigators could provide the data, and therefore, data from six identified studies were not included.<sup>9–14</sup> However, the results of a classical meta-analysis including all but one study<sup>14</sup> 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.<sup>5</sup> 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)<sup>8</sup> 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<sub>2</sub>O PEEP. However, the moderate PEEP group 6 to 8 cm H<sub>2</sub>O 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.<sup>6</sup> 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.

## Correspondence

Address correspondence to Dr. Serpa Neto: Department of Critical Care, Hospital Israelita Albert Einstein, Albert Einstein Avenue, 700 São Paulo, Brazil. aryserpa@terra.com.br. This article may be accessed for personal use at no charge through the Journal Web site, [www.anesthesiology.org](http://www.anesthesiology.org).

## References

1. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, Vallet B, Vincent JL, Hoefft A, Rhodes A; European Surgical Outcomes Study (EuSOS) group for the Trials groups of the European Society of Intensive Care Medicine and the European Society of Anaesthesiology: Mortality after surgery in Europe: A 7 day cohort study. *Lancet* 2012; 380:1059–65
2. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, Sabaté S, Mazo V, Briones Z, Sanchis J; ARISCAT Group: Prediction of postoperative pulmonary complications in a population-based surgical cohort. *ANESTHESIOLOGY* 2010; 113:1338–50
3. Serpa Neto A, Cardoso SO, Manetta JA, Pereira VG, Espósito DC, Pasqualucci Mde O, Damasceno MC, Schultz MJ: Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: A meta-analysis. *JAMA* 2012; 308:1651–9
4. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013; 369:428–37
5. Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A, Dionigi G, Novario R, Gregoretti C, Gama de Abreu M, Schultz MJ, Jaber S, Futier E, Chiaranda M, Pelosi P: Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. *ANESTHESIOLOGY* 2013; 118:1307–21
6. The PROVE Network Investigators: Higher *versus* lower positive end-expiratory pressure during general anaesthesia for open abdominal surgery—The PROVHILO trial. *Lancet* 2014; 384:495–503
7. Levin MA, McCormick PJ, Lin HM, Hosseinian L, Fischer GW: Low intraoperative tidal volume ventilation with minimal PEEP is associated with increased mortality. *Br J Anaesth* 2014; 113:97–108
8. Serpa Neto A, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network investigators: Protocol for a systematic review and individual patient data meta-analysis of benefit of so-called lung-protective ventilation settings in patients under general anesthesia for surgery. *Syst Rev* 2014; 3:2
9. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M: Protective ventilation attenuates postoperative pulmonary dysfunction in patients undergoing cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2000; 14:514–8
10. Koner O, Celebi S, Balci H, Cetin G, Karaoglu K, Cakar N: Effects of protective and conventional mechanical ventilation on pulmonary function and systemic cytokine release after cardiopulmonary bypass. *Intensive Care Med* 2004; 30:620–6
11. Michelet P, D'Journo XB, Roch A, Doddoli C, Marin V, Papazian L, Decamps I, Bregeon F, Thomas P, Auffray JP: Protective ventilation influences systemic inflammation after esophagectomy: A randomized controlled study. *ANESTHESIOLOGY* 2006; 105:911–9
12. Cai H, Gong H, Zhang L, Wang Y, Tian Y: Effect of low tidal volume ventilation on atelectasis in patients during general anesthesia: A computed tomographic scan. *J Clin Anesth* 2007; 19:125–9
13. Yang M, Ahn HJ, Kim K, Kim JA, Yi CA, Kim MJ, Kim HJ: Does a protective ventilation strategy reduce the risk of pulmonary complications after lung cancer surgery? A randomized controlled trial. *Chest* 2011; 139:530–7
14. Ahn HJ, Kim JA, Yang M, Shim WS, Park KJ, Lee JJ: Comparison between conventional and protective one-lung ventilation for ventilator-assisted thoracic surgery. *Anaesth Intensive Care* 2012; 40:780–8
15. Wrigge H, Uhlig U, Zinserling J, Behrends-Callsen E, Ottersbach G, Fischer M, Uhlig S, Putensen C: The effects of different ventilatory settings on pulmonary and systemic inflammatory responses during major surgery. *Anesth Analg* 2004; 98:775–81
16. Zupancich E, Paparella D, Turani F, Munch C, Rossi A, Massaccesi S, Ranieri VM: Mechanical ventilation affects



- inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: A randomized clinical trial. *J Thorac Cardiovasc Surg* 2005; 130:378–83
17. Reis Miranda D, Gommers D, Struijs A, Dekker R, Mekel J, Feelders R, Lachmann B, Bogers AJ: Ventilation according to the open lung concept attenuates pulmonary inflammatory response in cardiac surgery. *Eur J Cardiothorac Surg* 2005; 28:889–95
  18. Schilling T, Kozian A, Huth C, Bühling F, Kretzschmar M, Welte T, Hachenberg T: The pulmonary immune effects of mechanical ventilation in patients undergoing thoracic surgery. *Anesth Analg* 2005; 101:957–65
  19. Wolthuis EK, Choi G, Dassing MC, Bresser P, Lutter R, Dzoljic M, van der Poll T, Vroom MB, Hollmann M, Schultz MJ: Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. *ANESTHESIOLOGY* 2008; 108:46–54
  20. Lin WQ, Lu XY, Cao LH, Wen LL, Bai XH, Zhong ZJ: [Effects of the lung protective ventilatory strategy on proinflammatory cytokine release during one-lung ventilation]. *Ai Zheng* 2008; 27:870–3
  21. Weingarten TN, Whalen FX, Warner DO, Gajic O, Schears GJ, Snyder MR, Schroeder DR, Sprung J: Comparison of two ventilatory strategies in elderly patients undergoing major abdominal surgery. *Br J Anaesth* 2010; 104:16–22
  22. Sundar S, Novack V, Jervis K, Bender SP, Lerner A, Panzica P, Mahmood F, Malhotra A, Talmor D: Influence of low tidal volume ventilation on time to extubation in cardiac surgical patients. *ANESTHESIOLOGY* 2011; 114:1102–10
  23. Treschan TA, Kaisers W, Schaefer MS, Bastin B, Schmalz U, Wania V, Eisenberger CF, Saleh A, Weiss M, Schmitz A, Kienbaum P, Sessler DI, Pannen B, Beiderlinden M: Ventilation with low tidal volumes during upper abdominal surgery does not improve postoperative lung function. *Br J Anaesth* 2012; 109:263–71
  24. Memtsoudis SG, Bombardieri AM, Ma Y, Girardi FP: The effect of low *versus* high tidal volume ventilation on inflammatory markers in healthy individuals undergoing posterior spine fusion in the prone position: A randomized controlled trial. *J Clin Anesth* 2012; 24:263–9
  25. Unzueta C, Tusman G, Suarez-Sipmann F, Böhm S, Moral V: Alveolar recruitment improves ventilation during thoracic surgery: A randomized controlled trial. *Br J Anaesth* 2012; 108:517–24
  26. Maslow AD, Stafford TS, Davignon KR, Ng T: A randomized comparison of different ventilator strategies during thoracotomy for pulmonary resection. *J Thorac Cardiovasc Surg* 2013; 146:38–44
  27. Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–8
  28. Azevedo LC, Park M, Salluh JI, Rea-Neto A, Souza-Dantas VC, Varaschin P, Oliveira MC, Tierno PF, dal-Pizzol F, Silva UV, Knibel M, Nassar AP Jr, Alves RA, Ferreira JC, Teixeira C, Rezende V, Martinez A, Luciano PM, Schettino G, Soares M; ERICC (Epidemiology of Respiratory Insufficiency in Critical Care) investigators: Clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: A multicenter, prospective, cohort study. *Crit Care* 2013; 17:R63
  29. Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Peñuelas O, Abaira V, Raymondos K, Rios F, Nin N, Apezteguía C, Violi DA, Thille AW, Brochard L, González M, Villagomez AJ, Hurtado J, Davies AR, Du B, Maggiore SM, Pelosi P, Soto L, Tomacic V, D'Empaire G, Matamis D, Abroug F, Moreno RP, Soares MA, Arabi Y, Sandi F, Jibaja M, Amin P, Koh Y, Kuiper MA, Bülow HH, Zeggwagh AA, Anzueto A: Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med* 2013; 188:220–30
  30. Wolthuis EK, Vlaar AP, Choi G, Roelofs JJ, Juffermans NP, Schultz MJ: Mechanical ventilation using non-injurious ventilation settings causes lung injury in the absence of pre-existing lung injury in healthy mice. *Crit Care* 2009; 13:R1
  31. Hegeman MA, Hemmes SN, Kuipers MT, Bos LD, Jongsma G, Roelofs JJ, van der Sluijs KF, Juffermans NP, Vroom MB, Schultz MJ: The extent of ventilator-induced lung injury in mice partly depends on duration of mechanical ventilation. *Crit Care Res Pract* 2013; 2013:435236
  32. Menendez C, Martinez-Caro L, Moreno L, Nin N, Moral-Sanz J, Morales D, Cogolludo A, Esteban A, Lorente JA, Perez-Vizcaino F: Pulmonary vascular dysfunction induced by high tidal volume mechanical ventilation. *Crit Care Med* 2013; 41:e149–55
  33. Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, Hubmayr RD: Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 2004; 32:1817–24
  34. Jaber S, Coisel Y, Chanques G, Futier E, Constantin JM, Michelet P, Beaussier M, Lefrant JY, Allaouchiche B, Capdevila X, Marret E: A multicentre observational study of intra-operative ventilatory management during general anaesthesia: Tidal volumes and relation to body weight. *Anaesthesia* 2012; 67:999–1008
  35. Fernández-Pérez ER, Sprung J, Afessa B, Warner DO, Vachon CM, Schroeder DR, Brown DR, Hubmayr RD, Gajic O: Intraoperative ventilator settings and acute lung injury after elective surgery: A nested case control study. *Thorax* 2009; 64:121–7
  36. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1775–86
  37. Muscedere JG, Mullen JB, Gan K, Slutsky AS: Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med* 1994; 149:1327–34
  38. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G: Higher *vs* lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA* 2010; 303:865–73
  39. Pinsky MR: The hemodynamic consequences of mechanical ventilation: An evolving story. *Intensive Care Med* 1997; 23:493–503
  40. Wakabayashi K, Wilson MR, Tatham KC, O'Dea KP, Takata M: Volutrauma, but not atelectrauma, induces systemic cytokine production by lung-margined monocytes. *Crit Care Med* 2014; 42:e49–57
  41. Melo MF, Eikermann M: Protect the lungs during abdominal surgery: It may change the postoperative outcome. *ANESTHESIOLOGY* 2013; 118:1254–7