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Respiration and the Airway

RESPIRATION AND THE AIRWAY

Intraoperative positive end-expiratory pressure and postoperative pulmonary complications: a patient-level meta-analysis of three randomised clinical trials

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Abstract

Background: High intraoperative PEEP with recruitment manoeuvres may improve perioperative outcomes. We re-examined this question by conducting a patient-level meta-analysis of three clinical trials in adult patients at increased risk for postoperative pulmonary complications who underwent non-cardiothoracic and non-neurological surgery.

Methods: The three trials enrolled patients at 128 hospitals in 24 countries from February 2011 to February 2018. All patients received volume-controlled ventilation with low tidal volume. Analyses were performed using one-stage,

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two-level, mixed modelling (site as a random effect; trial as a fixed effect). The primary outcome was a composite of postoperative pulmonary complications within the first week, analysed using mixed-effect logistic regression. Pre-specified subgroup analyses of nine patient characteristics and seven procedure and care-delivery characteristics were also performed.

Results: Complete datasets were available for 1913 participants ventilated with high PEEP and recruitment manoeuvres, compared with 1924 participants who received low PEEP. The primary outcome occurred in 562/1913 (29.4%) participants randomised to high PEEP, compared with 620/1924 (32.2%) participants randomised to low PEEP (unadjusted odds ratio [OR]=0.87; 95% confidence interval [95% CI], 0.75–1.01; P=0.06). Higher PEEP resulted in 87/1913 (4.5%) participants requiring interventions for desaturation, compared with 216/1924 (11.2%) participants randomised to low PEEP (OR=0.34; 95% CI, 0.26–0.45). Intraoperative hypotension was associated more frequently (784/1913 [41.0%]) with high PEEP, compared with low PEEP (579/1924 [30.1%]; OR=1.87; 95% CI, 1.60–2.17).

Conclusions: High PEEP combined with recruitment manoeuvres during low tidal volume ventilation in patients undergoing major surgery did not reduce postoperative pulmonary complications.

Clinical trial registration: NCT03937375 (Clinicaltrials.gov).

Keywords: mechanical ventilation; PEEP; postoperative pulmonary complications; surgery

Editor's key points

- The putative benefits of high intraoperative PEEP with recruitment manoeuvres remain unclear.
- This patient-level meta-analysis examined whether postoperative pulmonary complications within the first week after surgery were reduced by high intraoperative PEEP.
- Heterogeneous outcome measures hampered the interpretation of the trials.
- High intraoperative PEEP was associated with fewer episodes of desaturation but more frequent intraoperative hypotension.
- High intraoperative PEEP with recruitment manoeuvres during low tidal volume ventilation does not reduce postoperative pulmonary complications.

Postoperative pulmonary complications occur frequently, and are associated with longer hospital length of stay, higher costs, and increased mortality.[1–3] Intraoperative low tidal volume potentially protects against postoperative pulmonary complications.[4–6] In contrast, the protective role of high PEEP with recruitment manoeuvres is less certain, as in most studies high PEEP with recruitment manoeuvres was combined with a low tidal volume, whereas in the control arm low PEEP was combined with a high tidal volume.

Higher tidal volumes during surgery is a contributing factor to the development of postoperative pulmonary complications, which obscures any potential effects of PEEP.[4–7] Although high PEEP with recruitment manoeuvres can protect the lungs against repetitive tidal recruitment and reduce the risk for intraoperative hypoxaemia, high PEEP may also cause overdistension and increase the risk for intraoperative hypotension.[7 8]

The results of three large multicentre, randomised clinical trials (PROVHILO [Protective ventilation during general anaesthesia for open abdominal surgery], iPROVE [Individualized perioperative open lung ventilatory strategy], and PROBESE [Protective intraoperative ventilation in obese patients]) appear to argue against the preventive use of high PEEP with recruitment manoeuvres in surgical patients at risk for postoperative pulmonary complications.[9–11] However, as there was significant heterogeneity amongst patients in these trials, and differences in usual care across participating hospitals, treatment effects in certain subgroups or particular settings cannot be ruled out. We therefore undertook an individual patient-level meta-analysis to examine whether high PEEP with recruitment manoeuvres may reduce postoperative pulmonary complications and adverse intraoperative events, compared with patients randomised to low PEEP.

Methods

This study was registered at Clinicaltrials.gov (NCT03937375). The protocol and statistical analysis plan of this meta-analysis were published before data pooling and start of the analysis.[12] The investigators of each trial provided the study protocols, case-report forms, and data dictionaries, which were compared for recoding if necessary. After receipt of the individual patient data, values were checked for missing and consistency, and data queries were sent to the investigators whenever needed. (Supplementary Table S1).

Original trial characteristics

The three original trials evaluated the effects of intraoperative high PEEP with recruitment manoeuvres on postoperative outcomes, with similar intraoperative care (Table 1).[9–11] Participation in the original studies required written informed consent and adhered to Good Clinical Practice.

Inclusion and exclusion criteria

No additional inclusion or exclusion criteria were used for this meta-analysis. The common inclusion criteria used in each trial were: (1) age ≥18 yr, (2) major surgery, and (3) Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score ≥26 (Table 1).

Primary outcome

The primary outcome was the proportion of patients developing one or more postoperative pulmonary complications within the first 7 postoperative days, defined as a collapsed composite of mild and severe respiratory failure (according to Pao_2 and SpO_2, and the degree of respiratory support), acute

Table 1 Characteristics of the included trials. *Based on the Cochrane risk of bias tool. ARDS, acute respiratory distress syndrome; ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ARR, absolute risk reduction; Cdyn, dynamic compliance; COPD, chronic obstructive pulmonary disease; iPROVE, individualized perioperative open lung ventilatory strategy; NIV, noninvasive ventilation; OLV, one-lung ventilation; PAH, pulmonary arterial hypertension; PBW, predicted body weight; PEPC, postoperative extrapulmonary complications; PPC, postoperative pulmonary complications; PROBESE, protective intraoperative ventilation in obese patients; PROVHILO, protective ventilation during general anaesthesia for open abdominal surgery; VCV, volume-controlled ventilation; VF, ventilatory frequency.

	PROVHILO	iPROVE	PROBESE
General			
Number of centres	30	21	77
Countries	International	Spain	International
Eligibility			
Inclusion criteria	1. Age ≥18 yr 2. Open abdominal surgery 3. ARISCAT ≥26	1. Age ≥18 yr 2. Major abdominal surgery 3. ARISCAT ≥26 4. Expected duration >2 h	1. Age ≥18 yr 2. Major surgery 3. ARISCAT ≥ 26 4. Expected duration >2 h 5. BMI ≥35 kg m^{-2}
Exclusion criteria	1. Laparoscopic surgery 2. BMI >40 kg m^{-2} 3. Pregnancy 4. Previous lung surgery 5. COPD with NIV or oxygen 6. Use of ventilation <30 days 7. ARDS 8. Intractable shock 9. Severe cardiac disease 10. Immunosuppression <60 days	1. BMI ≥35 kg m^{-2} 2. Pregnancy 3. Intracranial hypertension 4. Pneumothorax or giant bullae 5. COPD with NIV or oxygen 6. Use of ventilation <15 days 7. Moderate or severe ARDS 8. Heart failure	1. Neurosurgery or cardiac surgery 2. Need of OLV 3. Planned reintubation after surgery 4. Prone or lateral positioning 5. Pregnancy 6. Previous lung surgery 7. COPD with NIV or oxygen 8. Use of ventilation <30 days 9. Intractable shock 10. Severe cardiac disease 11. Immunosuppression <60 days 12. Severe PAH 13. Neuromuscular disease 14. Intracranial tumour or injury
Number of patients	894	967	1976
Outcome			
Primary	1. Incidence of PPC	1. Incidence of pulmonary and systemic complications	1. Incidence of PPC
Secondary	1. Intraoperative complications 2. Unexpected ICU admission 3. Hospital-free days at day 90 4. Postoperative wound healing 5. PEPC 6. Mortality	1. ICU length of stay 2. Hospital length of stay 3. ICU readmission 4. Hospital readmission 5. Mortality	1. Incidence of severe PPC 1. Intraoperative complications 2. Unexpected ICU admission 3. Hospital-free days at day 90 4. Postoperative wound healing 5. PEPC 6. Mortality
Intervention			
High PEEP arm	1. Mode: VCV 2. Tidal volume ≤8 ml kg PBW^{-1} 3. FiO_2 >0.40 to SpO_2 ≥92% 4. PEEP at 12 cm H_2O 5. Recruitment manoeuvres (directly after induction of anaesthesia, after any disconnection from the ventilator, and just before tracheal extubation) 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa	1. Mode: VCV 2. Tidal volume ≤8 ml kg^{-1} PBW 3. FiO_2 of 0.80 4. PEEP titrated by C_{dyn} 5. Recruitment manoeuvres (after intubation, and if respiratory system compliance decreased more than 10% and SpO_2 decreased to 96% or lower) 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa	1. Mode: VCV 2. Tidal volume ≤7 ml kg^{-1} PBW 3. FiO_2 ≥0.40 to SpO_2 ≥92% 4. PEEP at 12 cm H_2O 5. Recruitment manoeuvres (after endotracheal intubation, repeated every hour after any disconnection from the mechanical ventilator, and before the end of surgery) 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa

Continued

Table 1 Continued

	PROVHILO	iPROVE	PROBESE
Low PEEP arm	1. Mode: VCV 2. Tidal volume ≤8 ml kg^{-1} PBW 3. FiO_2 >0.40 to SpO_2 ≥92% 4. PEEP ≤2 cm H_2O 5. No recruitment manoeuvres 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa	1. Mode: VCV 2. Tidal volume ≤8 ml kg^{-1} PBW 3. FiO_2 of 0.80 4. PEEP at 5 cm H_2O 5. No recruitment manoeuvres 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa	1. Mode: VCV 2. Tidal volume ≤7 ml kg^{-1} PBW 3. FiO_2 >0.40 to SpO_2 ≥92% 4. PEEP at 4 cm H_2O 5. No recruitment manoeuvres 6. I:E at 1:2 7. VF to $etco_2$ 4.5–6.0 kPa
Sample size			
Power	80%	80%	80%
Effect size	7.5% ARR	12.5% ARR	10% ARR
Incidence in control	24%	25%	20%
Alpha	Two-sided 0.05	Two-sided 0•05	Two-sided 0•05
Interim analyses	Two at 300 and 600	Two at 460 and 600	Two at 50% and 75%
Stopping rules	O'Brien–Fleming	Modified Haybittle–Peto	Lan–DeMets alpha-spending function
Randomisation			
Sequence generation	Patient-level, permuted block randomisation with variable block sizes and stratified by centre	Patient-level, permuted block randomisation with variable block sizes	Patient-level, permuted block randomisation with variable block sizes and stratified by centre
Allocation concealment	Central Web-based, accessible 24 h day^{-1}	Central Web-based, accessible 24 h day^{-1}	Central Web-based, accessible 24 h day^{-1}
Blinding			
Methods	Double blinded with one investigator applying the intraoperative intervention and other doing the follow-up	Double blinded with one investigator applying the intraoperative intervention and other doing the follow-up	Double blinded with one investigator applying the intraoperative intervention and other doing the follow-up
Statistical methods			
Methods	Intention-to-treat	Modified intention-to-treat	Modified intention-to-treat
*Risk of bias**			
Random sequence generation	Low risk of bias	Low risk of bias	Low risk of bias
Allocation concealment	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of participants and personnel	High risk of bias	High risk of bias	High risk of bias
Blinding of outcome assessment	Low risk of bias	Low risk of bias	Low risk of bias
Incomplete outcome data	Low risk of bias	Low risk of bias	Low risk of bias
Selective reporting	Low risk of bias	Low risk of bias	Low risk of bias
Other source of bias	Low risk of bias	Low risk of bias	Low risk of bias

Table 2 Study participant characteristics. Data are mean (standard deviation), median (quartile 25–75) or *n* (%). *The Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score estimates the risk of postoperative pulmonary complications, with scores greater or equal than 45 indicating high risk. †Defined as haemoglobin ≤10 g dl^{-1}. ‡The ASA criteria for physical status include a classification for normal health (1), mild systemic disease (2), severe systemic disease (3), severe systemic disease that is a constant threat to life (4), and a moribund person who is not expected to survive without the operation (6). PPC, postoperative pulmonary complications.

	High PEEP (*n*=1913)	Low PEEP (*n*=1924)
Age (yr)	55.9 (15.6)	56.8 (15.3)
Range	(19–93)	(18–91)
Female sex	1058/1910 (55.4)	1046/1918 (54.5)
Height (cm)	166 (10)	166 (9)
Weight (kg)	96.3 (31.9)	95.0 (30.9)
BMI (kg m^{-2})	34.5 (10.7)	34.2 (10.5)
<30	756/1758 (43.0)	783/1761 (44.5)
30–35	143/1758 (8.1)	116/1761 (6.6)
≥35	859/1758 (48.9)	862/1761 (48.9)
ARISCAT score*	36.9 (9.6)	37.1 (9.7)
Intermediate	1604/1900 (84.0)	1586/1912 (82.5)
High	306/1900 (16.0)	336/1912 (17.5)
Risk factors for PPC		
SpO_2 (%)	97 (2)	97 (2)
≥96	1430/1898 (75.3)	1394/1905 (73.2)
91–95	452/1898 (23.8)	497/1905 (26.1)
<91	16/1898 (0.8)	14/1905 (0.7)
Respiratory infection within the past month	111/1903 (5.8)	94/1914 (4.9)
Anaemia†	123/1720 (7.2)	120/1732 (6.9)
Surgical incision		
Peripheral	126 (6.6)	126 (6.5)
Abdominal	1787 (93.4)	1798 (93.5)
Emergency procedure	30 (1.6)	28 (1.5)
ASA physical status‡		
1	101/1896 (5.3)	108/1903 (5.7)
2	972/1896 (51.3)	933/1903 (49.0)
3	808/1896 (42.6)	841/1903 (44.2)
4	14/1896 (0.7)	21/1903 (1.1)
5	1/1896 (0.1)	0/1903 (0.0)
Coexisting conditions		
Heart failure	133/1902 (7.0)	151/1914 (7.9)
Chronic obstructive pulmonary disease	113/1912 (5.9)	109/1923 (5.7)
Cancer	783/1906 (41.1)	817/1921 (42.5)
Preoperative haemoglobin (g dl^{-1})	13.2 (2.0)	13.2 (2.0)
Type of surgery		
Abdominal	1819/1911 (95.2)	1821/1923 (94.7)
Non-abdominal	92/1911 (4.8)	102/1923 (5.3)
Specific procedure		
Bariatric	557/1911 (29.1)	562/1923 (29.2)
Bladder or urology	107/1911 (5.6)	106/1923 (5.5)
Bowel	21/1911 (1.1)	27/1923 (1.4)
Colorectal	390/1911 (20.4)	384/1923 (20.0)
Gastric	106/1911 (5.5)	109/1923 (5.7)
Hepatic	170/1911 (8.9)	149/1923 (7.7)
Hernia	31/1911 (1.6)	32/1923 (1.7)
Kidney	20/1911 (1.0)	32/1923 (1.7)
Pancreatic	110/1911 (5.8)	120/1923 (6.2)
Gynaecology	91/1911 (4.8)	91/1923 (4.7)
Head and neck	24/1911 (1.3)	24/1923 (1.2)
Orthopaedic	35/1911 (1.8)	29/1923 (1.5)
Plastic	9/1911 (0.5)	23/1923 (1.2)
Vascular	35/1911 (1.8)	35/1923 (1.8)
Other gynaecology	10/1911 (0.5)	9/1923 (0.5)
Other urology	3/1911 (0.2)	4/1923 (0.2)
Others	192/1911 (10.0)	187/1923 (9.7)
Surgical approach		
Non-laparoscopic	870/1779 (48.9)	874/1782 (49.0)
Laparoscopic	909/1779 (51.1)	908/1782 (51.0)

respiratory distress syndrome (according to Berlin definition), pulmonary infection (according to a combined criteria of chest X-ray, fever white blood cell count and sputum), pleural effusion (according to chest radiography), atelectasis (according to chest radiography), pneumothorax (according to chest radiography), and bronchospasm (according to the presence of wheezing and use of bronchodilator). Details on individual components of the composite are shown in Supplementary Table S2g.

Secondary outcomes

Secondary outcomes included intraoperative complications including rescue for desaturation and hypotension; 'severe' postoperative pulmonary complications in which mild respiratory failure was ignored; and 'major postoperative complications', a composite consisting of 'severe' postoperative pulmonary complications, postoperative sepsis or septic shock and postoperative acute kidney injury. Unexpected need for ICU admission, hospital length of stay, 7-day mortality, and in-hospital mortality were additional secondary endpoints.

Statistical analyses

All analyses were conducted on an intention-to-treat basis (according to the original group allocation in the original trials) and performed using one stage, two-level (patients nested in study sites, within the trials), mixed modelling with site as random effect and trial as a fixed effect. Heterogeneity between trials was determined by fitting a fixed interaction term between treatment and trial, whereas overall treatment effect is reported with trial treated as a fixed effect and site treated as a random effect. The primary outcome (and other binary outcomes) was analysed using mixed-effect logistic regression and reported as odds ratio and 95% confidence intervals (CIs). Hospital length of stay was analysed with mixed-effect generalised linear models considering an inverse Gaussian distribution (according to best fit) and reported as mean difference and 95% CI. Analyses were not adjusted for strong prognostic covariates.

To determine if the relationship between treatment and the primary outcome differs between pre-specified, clinically important subgroups, fixed interaction terms between treatment and subgroup were added in the unadjusted model for the primary outcome described above. To further ascertain if the treatment–subgroup interaction varied between the three studies, a three-way fixed interaction between trial, treatment, and subgroup were also reported. Pre-specified subgroups according to baseline patient characteristics were age, gender, BMI, baseline SpO_2, surgical risk (ASA physical status, ranging from 1 to 5 with higher scores indicating greater surgical risk), risk for postoperative pulmonary complications (ARISCAT score, ranging from 0 to 123 with higher scores indicating greater risk), chronic obstructive pulmonary disease, cancer and preoperative anaemia. Pre-specified subgroups according to procedure and intervention characteristics were type of procedure (non-laparoscopic or laparoscopic), surgical site (abdominal or non-abdominal), urgency of surgery (emergency or non-emergency), type of PEEP selection (fixed or titrated), and use of postoperative intervention. Finally, pre-specified subgroups according to care-delivery factors were day of start of anaesthesia (weekday or weekend) and time of start of anaesthesia (day or night).

As sensitivity analyses, the effect of the intervention on the primary and secondary outcomes were re-estimated using the same mixed-effect models described above but adjusted for pre-specified baseline covariates of sex (included as a categorical variable), age, baseline SpO_2, ARISCAT score, and BMI (included as continuous variables). Because the primary outcome was a composite outcome, additional sensitivity analyses were also performed (described in detail in Supplement 1). The following analyses were performed: (1) a count analysis (the number of positive component events, i.e. 'count' across the composite); (2) an individual component analysis (the effect of the intervention on each component of the composite); (3) a common effect test (estimation of the common effect odds ratio across the individual components of the composite); (4) an average relative effect test (estimation of a distinct treatment effect for each component of the composite); and (5) a heterogeneity of treatment effect (estimation of heterogeneity of treatment effect across components of the composite). A *post-hoc* sensitivity analysis was performed assessing the impact of the intervention on the primary outcome after adjustment for sex, emergency procedure, need of vasopressor (as categorical variables), age, baseline SpO_2, ARISCAT score, BMI, duration of surgery, blood loss, and total fluid intake (as continuous variables).

All analyses were performed using the R (R, version 3.6.0; Core Team, Vienna, Austria, 2016) software, and a two-sided alpha level of 0.05 was considered. Complete-case analysis was used for all outcomes because data were missing for less than 1% for all outcomes. In addition to the unadjusted *P*-values for secondary outcomes, a Holm–Bonferroni procedure was applied to control the family-wide error rate to the *P* values for all 14 secondary outcomes. The subgroup analyses were not adjusted for multiple comparisons; with 16 pre-specified subgroup analyses, one significant interaction test would be expected by chance alone.

Results

Participant characteristics

From February 2011 through February 2018, the three original studies enrolled 3925 patients at 128 hospitals in 24 countries worldwide with 3837 patients eligible for inclusion in the patient-level meta-analysis. Overall, 1913 patients received high PEEP and recruitment manoeuvres (high PEEP), compared with 1924 patients who received low PEEP (low PEEP). (Table 2; Supplementary Tables S3 and S4). Intraoperative characteristics were similar between participants randomised to high *vs* low PEEP (Table 3). Peak pressure was higher and driving pressure was lower in the high PEEP group (Supplementary Fig. S5). Recruitment manoeuvres were almost universal in the high PEEP group, compared with <0.5% in the low PEEP group (Supplementary Fig. S5). Additional cardiorespiratory data are provided in supplementary data (Supplementary Figs S6 and S7). Postoperative pulmonary complications occurred most commonly (93%) within in the first 3 days after surgery.

Primary outcome: pulmonary morbidity after surgery

One or more postoperative pulmonary complications within the first 7 days after surgery (Table 4) occurred in 562/1913

Table 3 Intraoperative management. Data are mean (standard deviation), median (quartile 25–75) or *n* (%). *Unless when indicated, absolute difference is the mean difference calculated from a mixed-effect linear model with trials as fixed effect and sites as random effect. †Any recruitment during surgery. In iPROVE, protocol mandated only one recruitment manoeuvre after intubation. ‡Absolute difference is the risk difference calculated from a mixed-effect generalised linear model considering a binomial distribution with an identity link and with trials as fixed effect and sites as random effect. ¶Driving pressure calculated as plateau pressure − PEEP. §Calculated as the difference in the use of balanced anaesthesia. FiO_2, inspired fraction of oxygen; SpO_2, pulse oximetry; $ETco_2$, partial end-tidal carbon dioxide.

	High PEEP ($n = 1913$)	Low PEEP ($n = 1924$)	Absolute difference* (95% CI)	*P*-value
Tidal volume (ml kg^{-1} PBW)				
After induction	7.6 (1.3)	7.6 (0.9)	0.03 (−0.04 to 0.09)	0.41
First hour	7.7 (1.3)	7.6 (0.7)	0.07 (0.01–0.13)	0.02
Last hour	7.7 (1.5)	7.6 (0.8)	0.09 (0.02–0.16)	0.008
PEEP (cm H_2O)				
After induction	10.7 (3.3)	3.2 (1.7)	7.51 (7.37–7.66)	<0.001
First hour	11.5 (2.0)	3.8 (1.8)	7.73 (7.62–7.84)	<0.001
Last hour	11.5 (2.2)	3.8 (1.9)	7.72 (7.60–7.84)	<0.001
Recruitment manoeuvres†				
After induction	1885 (98.5)	6 (0.3)	98.20 (97.62–98.75)‡	<0.001
First hour	1329 (69.5)	8 (0.4)	69.12 (67.51–70.74)‡	<0.001
Last hour	1402 (73.3)	7 (0.4)	72.96 (71.48–74.44)‡	<0.001
Number − median (IQR)	3 (1–4)	0 (0–0)	3.18 (3.11–3.25)	<0.001
Peak pressure (cm H_2O)				
After induction	23.3 (5.7)	20.9 (6.1)	2.33 (2.02–2.63)	<0.001
First hour	26.2 (5.6)	23.4 (6.8)	2.81 (2.49–3.12)	<0.001
Last hour	25.6 (5.4)	22.7 (6.5)	2.88 (2.58–3.18)	<0.001
Driving pressure¶ (cm H_2O)				
After induction	11.3 (4.6)	15.4 (5.1)	−4.15 (−4.57 to −3.73)	<0.001
First hour	11.8 (4.5)	16.4 (5.7)	−4.68 (−5.03 to −4.33)	<0.001
Last hour	11.0 (4.8)	15.4 (5.7)	−4.46 (−4.80 to −4.11)	<0.001
Ventilatory frequency (bpm)				
After induction	12.9 (2.7)	13.2 (2.6)	−0.29 (−0.42 to −0.17)	<0.001
First hour	14.0 (3.5)	14.2 (3.5)	−0.19 (−0.33 to −0.05)	0.007
Last hour	14.8 (4.0)	15.0 (4.1)	−0.19 (−0.35 to −0.02)	0.02
FiO_2 (%)				
After induction	64.4 (21.9)	63.7 (21.3)	0.83 (−0.02 to 1.68)	0.05
First hour	53.7 (16.9)	55.3 (16.9)	−1.59 (−2.13 to −1.05)	<0.001
Last hour	54.0 (17.6)	56.5 (18.3)	−2.60 (−3.24 to −1.95)	<0.001
SpO_2 (%)				
After induction	98.7 (1.7)	98.2 (2.4)	0.46 (0.34–0.58)	<0.001
First hour	98.6 (1.7)	97.7 (2.4)	0.86 (0.75–0.97)	<0.001
Last hour	98.8 (2.1)	98.2 (2.2)	0.65 (0.53–0.77)	<0.001
$ETco_2$ (kPa)				
After induction	4.9 (0.7)	4.9 (0.6)	0.02 (−0.01 to 0.07)	0.23
First hour	5.2 (0.7)	5.1 (0.7)	0.10 (0.06–0.13)	<0.001
Last hour	5.3 (0.7)	5.2 (0.7)	0.09 (0.05–0.13)	<0.001
Heart rate (beats min^{-1})				
After induction	75.2 (15.7)	74.3 (14.5)	0.87 (−0.16 to 1.89)	0.10
First hour	71.5 (13.8)	71.3 (14.1)	0.31 (−0.61 to 1.24)	0.51
Last hour	73.0 (13.4)	73.4 (13.5)	−0.36 (−1.30 to 0.57)	0.44
Mean arterial pressure (mm Hg)				
After induction	83.0 (18.3)	81.8 (16.8)	1.28 (0.20–2.37)	0.02
First hour	81.4 (14.4)	81.0 (14.5)	0.40 (−0.49 to 1.29)	0.38
Last hour	79.7 (13.3)	80.0 (13.4)	−0.26 (−1.07 to 0.55)	0.53
Type of anaesthesia				
Total intravenous	204/1912 (10.7)	213/1922 (11.1)	0.30 (−1.37 to 1.97)‡,§	0.72
Balanced	1708/1912 (89.3)	1709/1922 (88.9)		
Epidural analgesia	581/1911 (30.4)	560/1921 (29.2)	0.95 (−1.27 to 3.18)‡	0.40
Neuromuscular block				
Monitoring	921/1896 (48.6)	917/1907 (48.1)	0.55 (−1.47 to 2.58)‡	0.59
Residual curarisation	309/837 (36.9)	273/847 (32.2)	4.59 (1.64–7.55)‡	0.002
Total fluids (ml)	2000 (1300–3000)	2000 (1250–2866)	91.14 (9.39–172.92)	0.03
Crystalloids	2000 (1200–2500)	1800 (1075–2500)	60.53 (−9.97 to 131.05)	0.09
Synthetic colloids	0 (0–500)	0 (0–312)	19.82 (−2.84 to 42.47)	0.09
Urine output (ml)	200 (100–400)	200 (100–410)	−28.19 (−49.83 to −6.55)	0.01
Transfusion of blood products	146/1913 (7.6)	169/1924 (8.8)	−1.10 (−2.76 to 0.56)‡	0.19
Packed red blood cells	81/1433 (5.7)	107/1436 (7.5)	−1.75 (−3.45 to −0.05)‡	0.04
Fresh frozen plasma	35/1433 (2.4)	41/1436 (2.9)	−0.43 (−1.53 to 0.68)‡	0.45
Platelets	5/1433 (0.3)	12/1436 (0.8)	−0.48 (−1.04 to 0.07)‡	0.09
Blood loss (ml)	150 (50–350)	150 (50–300)	8.83 (−34.40 to 52.11)	0.69
Duration of surgery (min)	179 (128–240)	180 (127–230)	5.21 (0.17–10.24)	0.04
Duration of anaesthesia (min)	210 (160–300)	210 (160–280)	5.11 (−1.69 to 11.90)	0.14

Table 4 Primary and secondary outcomes. Data are mean (standard deviation), median (quartile 25–75) or *n* (%). All models are mixed-effect models with site as random effect and trial as a fixed effect. *P-value estimated from a fixed interaction term between treatment and trial in the model. †Effect estimate is odds ratio. 95% confidence intervals and *P*-values calculated with a mixed-effect logistic regression models with site as random effect and trial as a fixed effect. ‡Adjusted intraclass correlation coefficient and condition intraclass correlation coefficient of 0.239 and 0.238, respectively. ¶Effect estimate is mean difference. 95% confidence interval and *P*-values calculated with a mixed-effect generalised linear regression model considering an inverse Gaussian distribution with site as random effect and trial as a fixed effect. §Effect estimate is hazard ratio. 95% confidence intervals and *P*-values calculated with a (shared frailty) Cox proportional hazard model with site as random effect and trial as a fixed effect. ARDS, acute respiratory distress syndrome; IQR, inter-quartile range.

	High PEEP (*n*=1913)	Low PEEP (*n*=1924)	Unadjusted effect		
			Effect estimate (95% CI)	P-value (overall)	P-value* (trials)
Primary outcome					
Postoperative pulmonary complications	562/1905 (29.5)	620/1918 (32.3)	0.87 (0.75–1.01)†,‡	0.06	0.14
Mild respiratory failure	339/1904 (17.8)	377/1918 (19.7)	0.88 (0.74–1.04)†	0.13	0.03
Severe respiratory failure	130/1904 (6.8)	140/1918 (7.3)	0.93 (0.72–1.20)†	0.55	0.54
Acute respiratory distress syndrome	17/1905 (0.9)	22/1919 (1.1)	0.81 (0.42–1.54)†	0.51	0.61
Pulmonary infection	83/1905 (4.4)	83/1919 (4.3)	1.03 (0.74–1.43)†	0.88	0.42
Pleural effusion	174/1905 (9.1)	174/1919 (9.1)	1.05 (0.83–1.33)†	0.70	0.69
Atelectasis	190/1905 (10.0)	236/1919 (12.3)	0.79 (0.63–0.99)†	0.04	0.40
Pneumothorax	12/1905 (0.6)	11/1919 (0.6)	1.05 (0.46–2.42)†	0.91	0.08
Bronchospasm	29/1904 (1.5)	33/1918 (1.7)	0.89 (0.53–1.50)†	0.67	0.64
Secondary outcomes					
Severe postoperative pulmonary complications	396/1905 (20.8)	450/1918 (23.5)	0.85 (0.72–1.00)†	0.05	0.78
Extrapulmonary complications	284/1905 (14.9)	285/1919 (14.9)	0.99 (0.82–1.20)	0.96	0.44
Systemic inflammatory response syndrome	187/1905 (9.8)	188/1919 (9.8)	1.00 (0.80–1.25)†	0.99	0.58
Sepsis	60/1905 (3.1)	71/1919 (3.7)	0.86 (0.61–1.23)†	0.42	0.22
Septic shock	24/1905 (1.3)	29/1919 (1.5)	0.84 (0.48–1.45)†	0.53	0.75
Acute kidney injury	118/1905 (6.2)	137/1920 (7.1)	0.87 (0.66–1.13)†	0.30	0.51
Major complications	464/1905 (24.4)	516/1919 (26.9)	0.87 (0.75–1.02)†	0.10	0.90
Intraoperative adverse events					
Hypotension	784 (41.0)	579 (30.1)	1.87 (1.60–2.17)†	<0.001	0.03
Rescue for desaturation	87 (4.5)	216 (11.2)	0.34 (0.26–0.45)†	<0.001	0.03
Need for vasoactive drugs	1030/1903 (54.1)	936/1915 (48.9)	1.40 (1.19–1.65)†	<0.001	0.03
Unexpected ICU admission	167/1895 (8.8)	156/1908 (8.2)	1.15 (0.87–1.53)†	0.33	0.90
Hospital length of stay (days)	9.0 (10.8)	9.1 (11.4)	−0.00 (−0.03 to 0.03)¶	0.96	0.006
Median (IQR)	6 (3–10)	6 (3–10)			
Mortality					
7-day	7/1899 (0.4)	5/1909 (0.3)	1.40 (0.45–4.44)§	0.56	0.10
In-hospital	26/1899 (1.4)	21/1908 (1.1)	1.25 (0.70–2.23)†	0.45	0.63

(29.4%) participants randomised to receive high PEEP, compared with 620/1924 (32.2%) participants randomised to receive low PEEP (odds ratio=0.87; 95% CI, 0.75–1.01]; *P*=0.06).

There was no treatment effect between studies (*P*=0.14). Among the eight components of the composite endpoint, only atelectasis occurred less often in the high PEEP group (odds ratio=0.79; 95% CI, 0.63–0.99; *P*=0.04). In additional sensitivity analyses, after adjustment for confounders, complications between high *vs* low PEEP were not different (Supplementary Tables S5, S6, and S8).

Secondary outcomes

Severe postoperative pulmonary complications, major postoperative complications, unexpected ICU admission, and hospital length of stay mortality were not different between participants receiving high *vs* low PEEP (Table 4; Supplementary Table 5). Intraoperative rescue for desaturation was less frequent with high PEEP, although this treatment was associated with more hypotension and need for vasoactive drugs occurred more frequently with high PEEP (Table 4; Supplementary Fig. S9).

Prespecified subgroup analyses

Of nine pre-specified patient characteristics evaluated in the subgroup analyses, none had significant interactions (Fig. 1). Among the seven pre-specified procedure and care-delivery characteristics subgroup analyses (Fig. 2), only a significant interaction between PEEP and type of surgery was found, with better outcomes in patients undergoing laparoscopic surgery randomised to high PEEP with recruitment manoeuvres.

Discussion

This patient-level meta-analysis of three multicentre randomised clinical trials of intraoperative ventilation in patients undergoing general anaesthesia for surgery provides a more in-depth analysis with greater power compared with the individual studies and earlier conventional meta-analysis of studies of high PEEP *vs* low PEEP. During protective tidal volume ventilation, compared with intraoperative low PEEP, high PEEP with recruitment manoeuvres did not significantly reduce postoperative pulmonary complications. Intraoperative rescue for desaturation occurred more frequently in

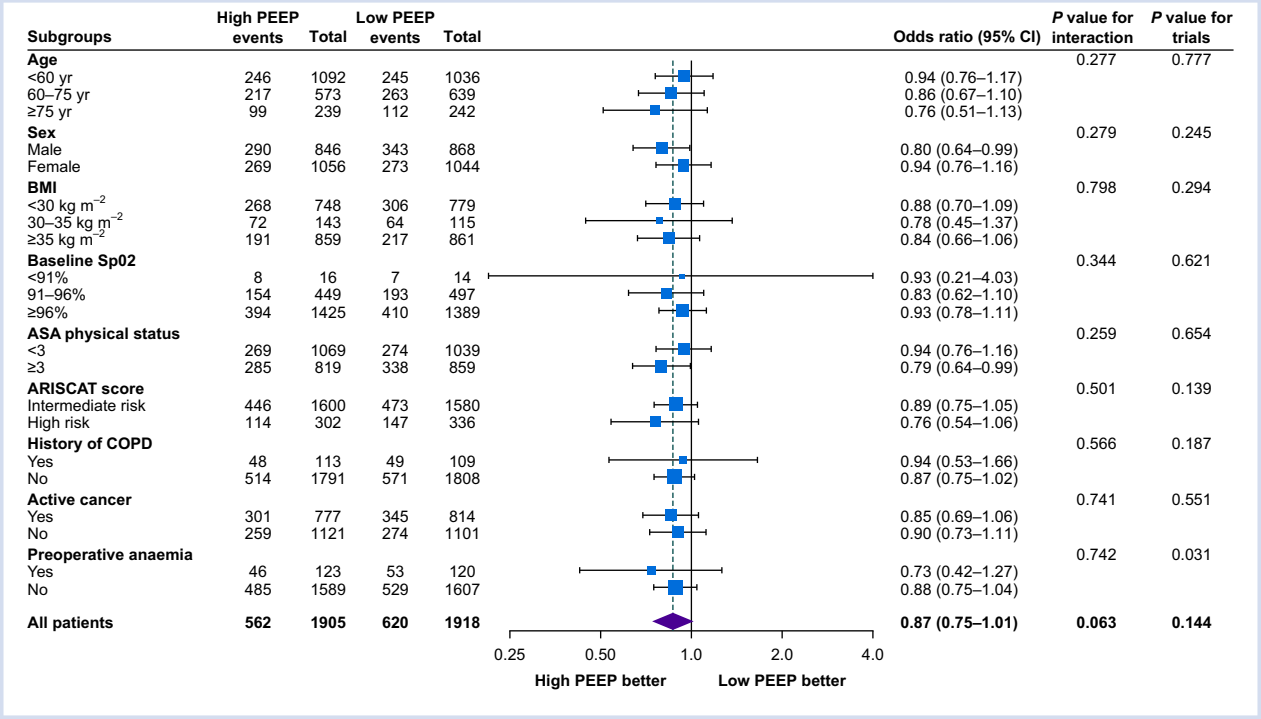

Fig 1. Postoperative pulmonary complications according to patient characteristics subgroups. Unadjusted odds ratio calculated from a mixed-effect logistic regression with trial treated as a fixed effect and site treated as a random effect. *P* values for the trial were calculated from a three-way fixed interaction between trial, treatment, and subgroup. The size of the square corresponds to the number of patients in each subgroup. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

patients in the low PEEP group, and hypotension and need for vasoactive drugs was more common in patients in the high PEEP group. These findings were consistent with the results of the original studies[9–11] and conventional meta-analyses[6,13–15].There was no evidence for any trial-specific effect.

Mechanical ventilation and general anaesthesia with muscle paralysis cause changes in lung morphology and reductions in lung volume and atelectasis that may impact adversely on intraoperative pulmonary mechanics and gas exchange.[16,17] Atelectasis and airway closure during surgery may lead to lung injury, increasing the risk of postoperative pulmonary complications.[18] The use of intraoperative high PEEP with recruitment manoeuvres prevents development of atelectasis,[19] homogenises ventilation,[20] minimises the risk of atelectrauma,[21] and decreases the driving pressure.[22] However, despite the appealing physiological rationale, no study to date was able to demonstrate improved patient-centred postoperative outcomes.

Concerns about the three original studies included the possibility that they included a low proportion of patients at 'sufficient' risk for postoperative pulmonary complications who may be expected to benefit most from preventive use of high PEEP.[23–25] The current analysis did not confirm the idea that these patients benefit more from preventive high PEEP with recruitment manoeuvres. We did find an interaction between high PEEP/recruitment manoeuvres and type of surgery, suggesting benefit in patients undergoing laparoscopic surgery. However, given the large number of subgroups analyses performed, this finding needs to be interpreted with caution and confirmed in future studies. With 16 subgroup analyses, it is expected that one analysis could be significant by chance alone. However, as a considerable number of patients are submitted to laparoscopic procedures, the possibility of a beneficial effect of high PEEP in this group should be investigated further.

In the three original studies, the event rate of severe pulmonary complications was mainly accounted for by the need for supplementary oxygen after surgery (SpO_2 <92% in room air).[23–25] In our analysis, the absolute number of severe postoperative pulmonary complications was similar between high *vs* low PEEP. Our findings regarding intraoperative events were also consistent with previous reports.[1,2,9–11,20] Intraoperative high PEEP with recruitment manoeuvres prevented desaturation but at the expense of a higher risk for hypotension. Further studies are necessary to determine the most acceptable trade-offs between PEEP and haemodynamic compromise.

Lower driving pressure may be lung protective and lead to better outcomes.[26–28] In our analysis, lower driving pressure was evident after high PEEP, compared with low PEEP. Nevertheless, this reduction was not associated with better postoperative outcome, despite the expectations raised by the results of previous observational studies.[26–29] It is important to emphasise, though, that among the original trials from which the current study used the individual patient data,[9–11] only one was designed to test a strategy aiming at maximising respiratory compliance.[10] Therefore, it cannot be ruled out that an individual titration of PEEP according to the lowest

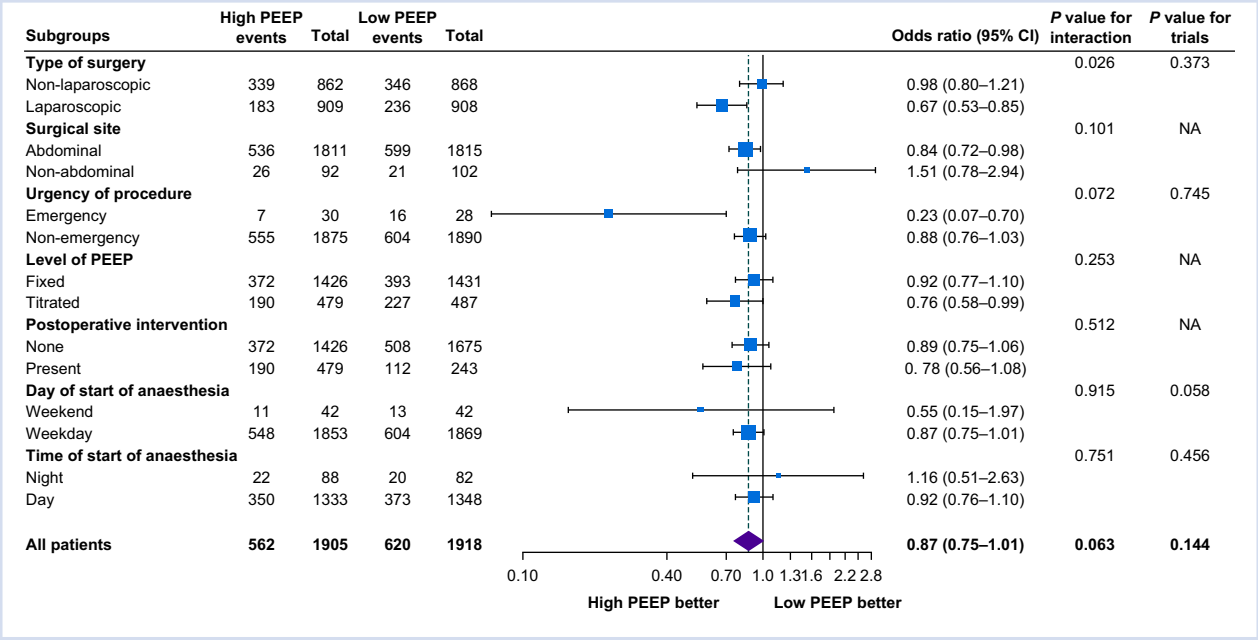

Fig 2. Postoperative pulmonary complications according to procedure and care-delivery subgroups. Unadjusted odds ratio calculated from a mixed-effect logistic regression with trial treated as a fixed effect and site treated as a random effect. *P* values for the trial were calculated from a three-way fixed interaction between trial, treatment, and subgroup. The size of the square corresponds to the number of patients in each subgroup. NA, not computed because one of the subgroups is available only in one of the trials; CI, confidence interval.

driving pressure would not lead to different results. In fact, a multicentre trial addressing the question whether individual titration of PEEP according to the driving pressure, as compared with a fixed low PEEP level, reduces postoperative pulmonary complications in patients undergoing open abdominal surgery is being conducted.[30]

In contrast to earlier observational studies[28,31] and small RCTs,[29,32] our study relies exclusively on random assignment, avoiding biases related to confounding by indication. Also, most RCTs so far focused on physiological endpoints, and not on clinically meaningful outcomes.[29,32] Nevertheless, there remain unresolved questions regarding moderate levels of PEEP (e.g. 6–8 cm H_2O), individualised PEEP titration, prolonged surgery, and laparoscopic procedures. Indeed, in two of the studies considered,[9,11] the PEEP used in the high PEEP group may have been too high, inducing overdistension rather than avoiding atelectasis.

This patient-level meta-analysis has important limitations. First, as in any meta-analysis, the results are built upon underlying internal and external validity of the three original studies. Second, although the overall sample size is large, some clinically important subgroups remained small, limiting the statistical power. Third, as the diagnosis of the components of postoperative pulmonary complications is based on clinical criteria, misclassification of patients might underestimate the observed effect; however, this factor should have equally affected the different groups analysed. Fourth, the capture of postoperative pulmonary complications after day 5 was possible but not mandatory in two of the trials,[9,11] and this could have led to underestimation of the true incidence of postoperative complications. However, the vast majority of postoperative pulmonary complications develop up to the third postoperative day,[1,10,18] and also here this factor should have equally affected both groups. Fifth, none of the trials were blinded for the intraoperative assessor, which may introduce bias. Sixth, PEEP level used in the control groups of the three original studies may not be representative of usual care in all settings. Seventh, the inclusion and exclusion criteria, the recruitment manoeuvre, and the PEEP selection was not homogeneous among the three original studies. Eight, the end of anaesthesia, and the transition from anaesthesia to awake is crucial in these patients, and this was not standardised across the trials included. Finally, the definitions of the components of the PPC were not completely standard across the included studies. However, no heterogeneity of treatment effect across trials was found.

In summary, in adults receiving general anaesthesia for non-neurological and non-cardiothoracic surgery, the combination of higher PEEP with recruitment manoeuvres (compared with low PEEP without recruitment manoeuvres) did not reduce postoperative pulmonary complications.

Authors' contributions

Full access to all of study data and responsibility for the integrity of the data and accuracy of the data analysis: NSC, ASN
Concept and design: all authors
Statistical analyses: NSC, ASN
Administrative, technical, or material support: NSC, PP, MGA, MJS, ASN
Supervision: CF, PP, MGA, MJS, ANS
The writing group vouches for the accuracy and completeness of the data and for the fidelity of the study to the protocol

All authors were involved in acquisition, analyses or interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content

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Declarations of interest

TB reported receiving personal fees from Comen Eletronics Technology Co. Ltd outside of the submitted work. MGA reported receiving grants and personal fees from Drägerwerk AG and GlaxoSmithKline and receiving personal fees from GE Healthcare outside of the submitted work. ASN reported receiving personal fees from Dräger outside of the submitted work. No other disclosures were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.02.039.

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