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Respiration and the Airway

Individualized PEEP to optimise respiratory mechanics during abdominal surgery: a pilot randomised controlled trial

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Abstract

Background: Higher intraoperative driving pressures (ΔP) are associated with increased postoperative pulmonary complications (PPC). We hypothesised that dynamic adjustment of PEEP throughout abdominal surgery reduces ΔP, maintains positive end-expiratory transpulmonary pressures (P_{tp_ee}) and increases respiratory system static compliance (C_{rs}) with PEEP levels that are variable between and within patients.

Methods: In a prospective multicentre pilot study, adults at moderate/high risk for PPC undergoing elective abdominal surgery were randomised to one of three ventilation protocols: (1) PEEP≤2 cm H_2O, compared with periodic recruitment manoeuvres followed by individualised PEEP to either optimise respiratory system compliance ($PEEP_{maxCrs}$) or maintain positive end-expiratory transpulmonary pressure ($PEEP_{Ptp\_ee}$). The composite primary outcome included intraoperative ΔP, P_{tp_ee}, C_{rs}, and PEEP values (median (interquartile range) and coefficients of variation [CV_{PEEP}]).

Results: Thirty-seven patients (48.6% female; age range: 47–73 yr) were assigned to control (PEEP≤2 cm H_2O; n=13), $PEEP_{maxCrs}$ (n=16), or $PEEP_{Ptp\_ee}$ (n=8) groups. The $PEEP_{Ptp\_ee}$ intervention could not be delivered in two patients. Subjects assigned to $PEEP_{maxCrs}$ had lower ΔP (median8 cm H_2O [7–10]), compared with the control group (12 cm H_2O [10–15]; P=0.006). $PEEP_{maxCrs}$ was also associated with higher P_{tp_ee} (2.0 cm H_2O [-0.7 to 4.5] *vs* controls: -8.3 cm H_2O [-13.0 to -4.0]; P≤0.001) and higher C_{rs} (47.7 ml cm H_2O [43.2–68.8] *vs* controls: 39.0 ml cm H_2O [32.9–43.4]; P=0.009). Individualised PEEP ($PEEP_{maxCrs}$ and $PEEP_{Ptp\_ee}$ combined) varied widely (median: 10 cm H_2O [8-15]; CV_{PEEP}=0.24 [0.14–0.35]), both between, and within, subjects throughout surgery.

Conclusions: This pilot study suggests that individualised PEEP management strategies applied during abdominal surgery reduce driving pressure, maintain positive P_{tp_ee} and increase static compliance. The wide range of PEEP observed suggests that an individualised approach is required to optimise respiratory mechanics during abdominal surgery.

Clinical trial registration: NCT02671721.

Keywords: lung compliance; mechanical ventilation; positive end-expiratory pressure; postoperative pulmonary complications; respiratory mechanics; ventilator-induced lung injury

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Editor's key points

- Higher intraoperative driving pressures are associated with a greater risk of developing postoperative pulmonary complications.
- In this pilot randomised controlled study, the authors explored whether individualised dynamic adjustment of PEEP during abdominal surgery reduces intraoperative driving pressure (amongst other measures of respiratory mechanics).
- Periodic recruitment manoeuvres to optimise either respiratory system compliance or positive end-expiratory transpulmonary pressure reduced intraoperative driving pressure.
- Given the wide variability in PEEP encountered, this pilot trial suggests that an individualised approach is required to optimise respiratory mechanics during abdominal surgery.

Postoperative pulmonary complications (PPCs) are associated with excess surgical morbidity and mortality.[1–4] The optimal PEEP level that minimises pulmonary atelectasis and overdistention, maximises oxygenation, limits hypotension, and reduces PPCs remains unclear, but is likely to be variable between individuals.[5] For patients without lung injury undergoing open abdominal surgery, a PEEP≤2 cm H_2O has been proposed as the standard of care.[6] This recommendation was derived from a single large trial[7] that compared two fixed PEEPs (≤2 *vs* 12 cm H_2O). Although a similar incidence of PPCs occurred between the two PEEP levels, intraoperative hypotension and vasopressor requirements were more frequent in patients receiving recruitment manoeuvres and PEEP=12 cm H_2O. However, lower PEEP has also been associated in other studies with higher rates of atelectasis,[8] major PPCs after abdominal surgery[9] and 30-day mortality.[10] Thus, criteria to set intraoperative PEEP that optimises respiratory system mechanics and reduces biological injury to improve perioperative outcomes is still required.

Inadequate PEEP leads to stiffer lungs and increased driving pressures (ΔP, calculated as plateau pressure: P_{plat}, minus PEEP), indicating increased lung strain.[11] Higher intraoperative ΔP has been associated with major PPCs, including barotrauma, lung oedema, reintubation, lung injury, and pneumonia.[12,13] Obesity, surgical position, and technique contribute to highly variable mechanical loads that the respiratory system encounters throughout surgery.

Dynamic PEEP individualisation throughout surgery, instead of a fixed PEEP, may optimise perioperative respiratory mechanics. The lack of an individualised approach may explain the lack of effect associated with a single PEEP titration performed at the beginning of surgery.[14,15] Two bedside approaches for PEEP individualisation have been proposed in critical care to minimise end-expiratory alveolar collapse[16–18]: maximisation of respiratory system static compliance (C_{rs})[19] and maintenance of a positive end-expiratory transpulmonary pressure (P_{tp_ee}, defined by the difference between PEEP and end-expiratory oesophageal pressure, P_{es_ee}, used as a surrogate of pleural pressure). These methods have not been compared during surgery.

Therefore, we designed a pilot study to assess these two PEEP individualisation methods during major abdominal surgery. We hypothesised that periodic PEEP individualisation throughout surgery would optimise respiratory mechanics by reducing ΔP, increasing C_{rs} and maintaining positive P_{tp_ee} with variable PEEP levels between and within patients. The effect of individualised PEEP strategies on circulating biomarkers for lung injury[20–24] was explored as a secondary outcome.

Methods

Institutional Review Board approval was obtained at each institution. The study was registered at clinicaltrials.gov (NCT02671721). The frequency of PPCs was erroneously registered as the original primary endpoint. The registration was subsequently modified to clarify that the primary aim of this feasibility study was to assess respiratory mechanics and to finalise the design of a subsequent full-scale trial addressing PPCs. Signed informed consent was obtained from all patients prior to randomisation and study procedures.

Study design

This was a three-site, prospective, randomised, controlled feasibility study comparing three different PEEP management protocols during general anaesthesia for abdominal surgery: two intervention groups with distinct methods to individualise intraoperative PEEP, and a control group with a constant ≤2 cm H_2O PEEP throughout surgery.[7] Full details on the methods are provided in the Supplementary material.

Inclusion criteria

Patients ≥18 years undergoing elective intraperitoneal abdominal or pelvic surgery expected to last ≥2 h at intermediate to high risk of PPCs (as defined by an 'Assess Respiratory Risk In Surgical Patients in Catalonia' (ARISCAT) risk score ≥26)[25] were eligible.

Exclusion criteria

Patients with predefined significant cardiopulmonary disease[26] and other conditions were ineligible.

Intraoperative ventilation

All subjects received volume-controlled ventilation (VCV) and lung protective settings[6]: tidal volume (V_T) 7±1 ml kg^{-1} of predicted body weight (PBW), 20% inspiratory pause, inspired oxygen fraction (FiO_2) starting at 0.4 and titrated for oxyhaemoglobin saturation (SpO_2)≥92%. An oesophageal pressure (P_{es}) balloon was placed according to current recommendations[27] in all patients for continuous monitoring of P_{es} and transpulmonary pressure (P_{tp}).[16] Correct positioning of the P_{es} balloon was ensured by continuous P_{es} monitoring identifying the presence of a cardiac artefact and P_{tp} changes during tidal ventilation, and confirmed by similar changes of P_{es} and airway pressure (P_{aw}) during an end-expiratory hold and thorax compression.[27] An *in vivo* calibration[28] was not performed. P_{es} was monitored continuously during PEEP titrations. P_{es_ee} was recorded in all patients at prespecified time points. End-inspiratory oesophageal pressure (P_{es_ei}) and derived variables were also studied in a subgroup of patients.

Study intervention

Randomisation was stratified by group and site. After randomisation, unblinded investigators performed the intervention. Treatment allocation was concealed from patients, postoperative care providers, and assessors of secondary outcomes. Patients randomised to the individualised PEEP groups also received preoperative education on reducing PPCs and postoperative strategies including incentive spirometry and early mobilisation. These interventions were monitored and supervised postoperatively. The control group could also receive these interventions as part of usual care, but was not supervised by the study team. Intraoperatively, patients were randomised to one of three PEEP strategies:

Control group (PEEP≤2 cm H_2O)

Received PEEP≤2 cm H_2O and no planned recruitment manoeuvres throughout the surgical procedure.[6]

Maximisation of respiratory system compliance ($PEEP_{maxCrs}$)

A recruitment manoeuvre (5 cm H_2O-stepwise increase up to 20 cm H_2O) was followed by a 3 cm H_2O decremental stepwise PEEP titration (see Supplementary materials for details). Static C_{rs} ($=V_T/[P_{plat}\text{-PEEP}]=V_T/\Delta P$) was assessed at each titration step and PEEP set at the level corresponding to the maximum C_{rs}. P_{es} was not used for PEEP-setting in this group. Patients

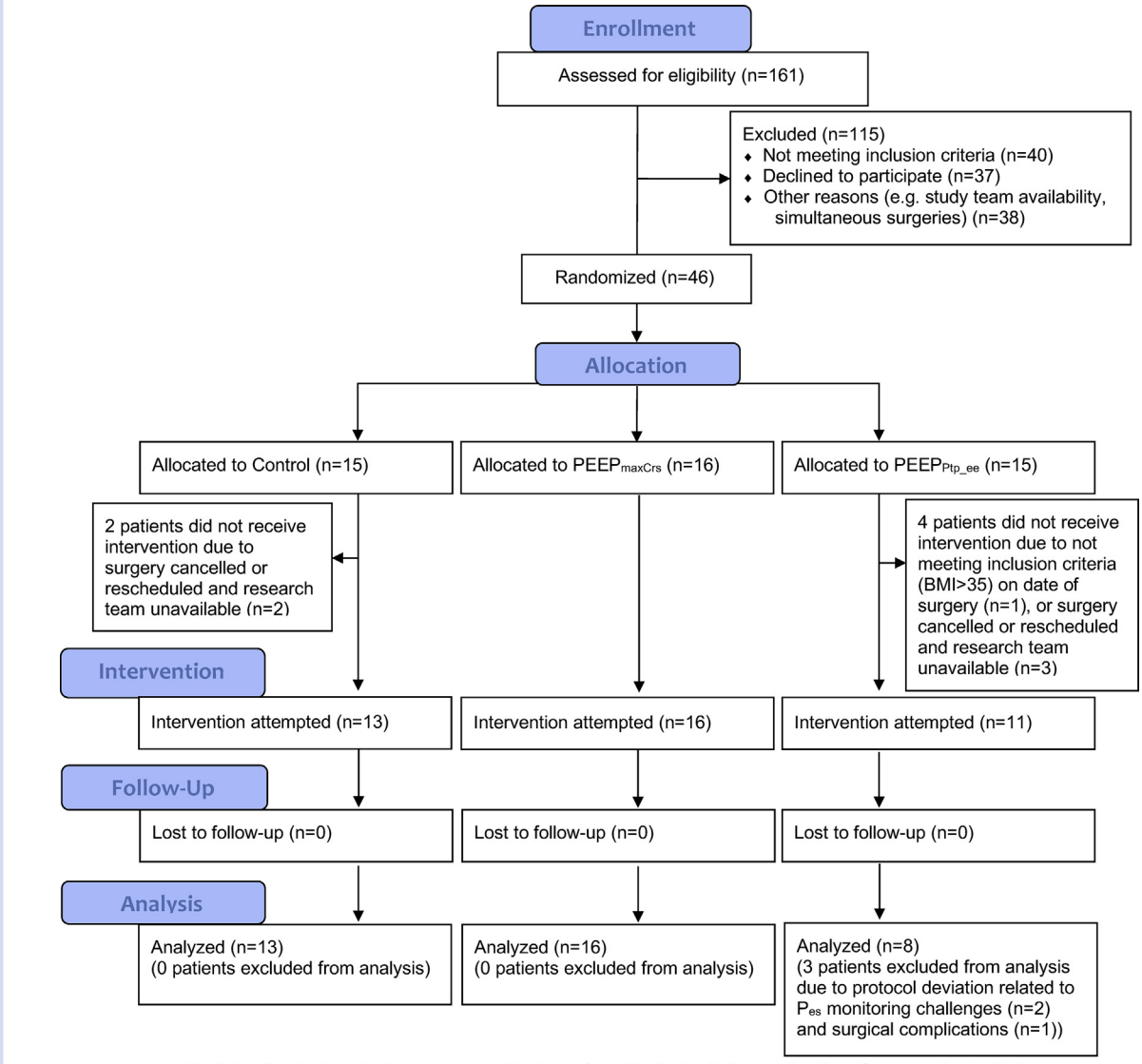

Fig 1. CONSORT flow diagram.

Table 1 Subject and procedure characteristics. Data represent median (Q1–Q3) or number of subjects (% of column). *P-values are calculated from Kruskal–Wallis test (for continuous variables) or Fisher's exact test (extended). [a]These differences between randomised subjects are considered owing to chance and *post hoc* comparisons not shown.

Variables	Control (n=13)	$PEEP_{maxCrs}$ (n=16)	$PEEP_{Ptp\_ee}$ (n=8)	P-value*
Demographics				
Age (yr)	69 (61–73)	60 (47–75)	55 (51–67)	0.501
Gender (male)	7 (54)	8 (50)	4 (50)	1.000
Body mass index (kg m^{-2})	26.4 (22.8–29.6)	23.4 (20.8–25.4)	24.7 (24.1–27.7)	0.187
Comorbidities				
Hypertension	10 (77)	2 (12)	2 (25)	0.002[a]
Coronary artery disease	0 (0)	2 (12)	0 (0)	0.496
Heart failure	1 (8)	1 (6)	0 (0)	1.000
Neurological disease	1 (8)	0 (0)	1 (12)	0.316
Chronic obstructive pulmonary disease	0 (0)	1 (6)	1 (12)	0.688
Asthma	1 (8)	2 (12)	2 (25)	0.695
Obstructive sleep apnoea	3 (23)	1 (6)	1 (12)	0.495
Smoking				0.534
Never	9 (69)	8 (50)	7 (88)	
Former	2 (15)	5 (31)	1 (12)	
Current <2 packs day^{-1}	2 (15)	3 (19)	0 (0)	
Renal disease	0 (0)	2 (12)	0 (0)	0.496
Liver disease	1 (8)	1 (6)	1 (12)	1.000
Alcohol use (previous yr)				0.374
Never	5 (38)	5 (31)	6 (75)	
Occasional	5 (38)	9 (56)	2 (25)	
Moderate	2 (15)	2 (12)	0 (0)	
Heavy	1 (8)	0 (0)	0 (0)	
Cancer	8 (62)	11 (69)	4 (50)	0.629
Gastro-oesophageal reflux disease	7 (54)	5 (31)	3 (38)	0.473
Diabetes mellitus	0 (0)	1 (6)	1 (12)	0.688
Total ARISCAT score	41 (41–41)	41 (35–49)	41 (38–41)	0.900
Surgical procedure				
Surgical service				0.717
General surgery	8 (62)	12 (75)	7 (88)	
Gynaecology	2 (15)	2 (12)	1 (12)	
Urology	3 (23)	1 (6)	0 (0)	
Other	0 (0)	1 (6)	0 (0)	
Surgical approach				0.416
Supra-umbilical	5 (38)	9 (56)	6 (75)	
Infra-umbilical	6 (46)	3 (19)	1 (12)	
Laparoscopic	2 (15)	4 (25)	1 (12)	
Surgery duration (min)	185 [144–236]	212 [179–340]	274 [200–343]	0.156
Anaesthesia duration (min)	243 [173–286]	277 [217–397]	322 [205–360]	0.279

receiving individualised PEEP had C_{rs} assessed before and after each PEEP individualisation intervention. Successful interventions were those resulting in maintained or increased C_{rs}. The successful C_{rs}-optimisation rate was calculated for each patient as the percentage of successful interventions over the total number of interventions performed.

Positive end-expiratory transpulmonary pressure ($PEEP_{Ptp\_ee}$)

Following the same standardised recruitment manoeuvre, absolute P_{es_ee} was assessed using the oesophageal balloon. PEEP was set to 1 cm H_2O greater than the P_{es_ee} (set PEEP=P_{es_ee}+1 cm H_2O).

Protocol

The intervention was started immediately after tracheal intubation and repeated hourly. Anaesthetic management otherwise followed routine clinical practice. Additional interventions were also performed when predefined events potentially associated with lung collapse were undertaken (application of surgical retractors, pneumoperitoneum insufflation/deflation, endotracheal tube disconnection, tracheal suctioning, Trendelenburg position). Before each PEEP adjustment, muscle paralysis was ensured and haemodynamic status were assessed. Full reversal of neuromuscular block guided by train-of-four neuromuscular monitoring was standardised.

Plasma biomarkers of lung injury

Blood was collected before (T_0), at the end of (T_{end}) and 24 h after (T_{24}) surgery. Plasma samples were analysed in duplicate by a blinded investigator for biomarkers of inflammatory lung injury (interleukin [IL]-6 and IL-8), epithelial injury (soluble form of the receptor for advanced glycation end-products [sRAGE] and club cell protein-16, [CC16]), endothelial injury (angiopoietin-2 [Ang-2]), and endothelial-derived coagulation activation (plasminogen activator inhibitor-1 [PAI-1]). Absolute biomarker levels and ratios relative to baseline (T_{end}/T_0, T_{24}/T_0) were calculated.

Table 2 Intraoperative characteristics. Data represent median (Q1–Q3) of the median values of each subject during surgery. ‡P-values are calculated from the Kruskal–Wallis test (for continuous variables) or Fisher's exact test (extended). For *post hoc* comparisons – we consider $P \leq 0.01667$ (=0.05/3) statistically significant – allowing for multiple comparisons. However, we also indicate for completeness all two-group comparisons where $0.01667 < P < 0.05$ as these would be considered significant if we had not adjusted for multiple comparisons. *P-value $0.01667 < P < 0.05$ compared with control; ^P-value $0.01667 < P < 0.05$ $PEEP_{Ptp\_ee}$ *vs* $PEEP_{maxCrs}$; **$P \leq 0.01667$ compared with control; ^^$P \leq 0.01667$ $PEEP_{Ptp\_ee}$ *vs* $PEEP_{maxCrs}$. [a]P_{es} values shown correspond to actual P_{es} measurements (absolute P_{es} levels). [b]Albumin was the only colloid administered to any study subject. [c]Includes only patients receiving any volume of albumin. PBW, predicted body weight.

Variables	Control (n=13)	$PEEP_{maxCrs}$ (n=16)	$PEEP_{Ptp\_ee}$ (n=8)	P-value‡
Respiratory variables				
Driving pressure (ΔP) (cm H_2O) (primary outcome)	12.0 (10.0–15.0)	8.0 (7.0–10.0)**	9.0 (7.8–10.1)*	0.011
Respiratory system static compliance (C_{rs}) (ml/cm H_2O)	39.0 (32.9–43.4)	47.7 (43.2–68.8)**	49.0 (44.6–58.7)**	0.010
Tidal volume (V_T) (ml/kg PBW)	6.7 (6.6–7.1)	7.1 (6.6–7.5)	6.9 (6.5–7.3)	0.810
Respiratory rate (RR) (bpm)	10.0 (10.0–12.0)	10.0 (10.0–12.0)	12.5 (11.0–13.5)	0.149
Peak inspiratory pressure (PIP) (cm H_2O)	18.0 (13.0–20.0)	21.0 (18.0–26.0)*	22.5 (21.5–27.0)**	0.007
Plateau pressure (P_{plat}) (cm H_2O)	14.7 (10.2–17.0)	17.3 (14.0–24.0)*	20.1 (18.0–23.5)**	0.006
PEEP (cm H_2O)	2.0 (0.0–2.0)	10.0 (6.5–15.0)**	11.0 (9.5–14.0)**	<0.001
PEEP coefficient of variation (CV_{PEEP})	0.00 (0.00–0.00)	0.25 (0.17–0.40)**	0.17 (0.14–0.23)**	<0.001
End-expiratory oesophageal pressure (P_{es_ee}) (cm H_2O)[a]	9.5 (6.0–14.8)	7.8 (5.6–10.7)	9.5 (8.8–12.3)	0.269
End-expiratory transpulmonary pressure (P_{tp_ee}) (cm H_2O)	-8.3 (-13.0–-4.0)	2.0 (-0.7–4.5)**	1.0 (1.0–2.3)**	<0.001
Inspired fraction of oxygen (FiO_2) (%)	40.0 (40.0–49.0)	40.0 (40.0–45.5)	43.0 (40.0–51.0)	0.821
Peripheral saturation of oxyhaemoglobin (SpO_2) (%)	98 (95–100)	99 (98.5–100)	99 (97.5–99.5)	0.353
Exhaled end-tidal partial pressure of CO_2 $P_{ET}CO_2$ (mmHg)	35.0 (34.0–37.0)	36.5 (33.5–39.0)	38.0 (37.0–39.0)**	0.048
Other vital signs				
Temperature (°C)	35.7 (35.5–36.2)	35.8 (35.2–36.8)	36.2 (35.8–36.6)	0.483
Heart rate (beats min^{-1})	64 (62–66)	70 (67–79)**	74 (71–80)**	0.007
Mean arterial blood pressure (mmHg)	84 (78–85)	80 (75–84)	82 (78–82)	0.535
Intraoperative fluid management				
Crystalloid volume (ml kg^{-1} h^{-1})	8.5 (6.0–9.3)	6.9 (6.1–10.6)	5.7 (4.9–8.9)	0.425
Albumin *n* (%)[b]	4 (31)	5 (31)	3 (38)	1.000
Albumin volume (ml kg^{-1} h^{-1})	1.3 (1.2–1.7)	2.5 (2.4–3.0)*	2.1 (1.4–2.2)	0.024
Any blood product *n* (%)				0.216
Packed red blood cells	0 (0)	0 (0)	0 (0)	
Fresh frozen plasma	0 (0)	0 (0)	1 (12)	
Platelets	0 (0)	0 (0)	0 (0)	
Estimated blood loss (ml)	100 (25–750)	188 (113–525)	575 (138–775)	0.407
Urine output (ml kg^{-1} h^{-1})	1.0 (0.6–1.7)	0.9 (0.6–1.2)	0.8 (0.5–1.7)	0.744
Vasoactive medications				
Vasoactive medications *n* (%)	12 (92)	16 (100)	8 (100)	0.387
Phenylephrine	9 (69)	15 (94)	8 (100)	0.071
Ephedrine	9 (69)	8 (50)	4 (40)	0.530
Vasopressin	2 (15)	2 (13)	1 (13)	0.970
Total vasoactive doses				
Phenylephrine (μg)	850 (0–5060)	1250 (630–3559)	6922 (3113–20 548)	0.064
Ephedrine (mg)	15 (0–30)	5 (0–17.5)	2.5 (0–17.5)	0.455
Vasopressin units	0 (0–0)	0 (0–0)	0 (0–0)	0.963

Primary outcome

The primary outcome comprised four measurements:

(1) the median intraoperative ΔP, calculated as P_{plat} measured at the end of the 20% inspiratory pause, minus PEEP;
(2) P_{tp_ee} (PEEP minus P_{es_ee};
(3) C_{rs} ($=V_T/(P_{plat}\text{-PEEP})=V_T/\Delta P$);
(4) PEEP median and coefficient of variation (CV_{PEEP}) (a joint outcome).

Of the four primary outcomes, we focused on ΔP because of its supported clinical relevance on PPCs.[12,13]

Secondary outcomes

Secondary outcomes were:

1. Intraoperative gas exchange variables;
2. Plasma levels of selected biomarkers of lung injury;
3. Postoperative pulmonary complications within 7 days after surgery (defined by established criteria from previous trials[25,29,30]).

Statistical analyses

Collected variables (e.g. subject characteristics, comorbidities, intraoperative respiratory, and other perioperative parameters, plasma biomarkers levels) were summarised as median (first quartile [Q1]- third quartile [Q3]) or number of patients (percentage), as appropriate. Non-parametric tests were used to avoid normality assumptions. We compared the outcomes and plasma concentrations and ratios of biomarkers from the three groups using the Kruskal–Wallis test (continuous variables) or Fisher's exact test extended to three groups (categorical variables). For the four primary (composite) endpoints, we used a Bonferroni adjustment for the overall test. For PEEP values, we required both median PEEP level and CV_{PEEP} to meet statistical significance to consider this joint endpoint as different accross the groups. We used Bonferroni adjustment for *post hoc* pairwise comparisons when the overall test was statistically significant. Two-tailed analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA). For the four primary (composite) outcomes, a significance level of

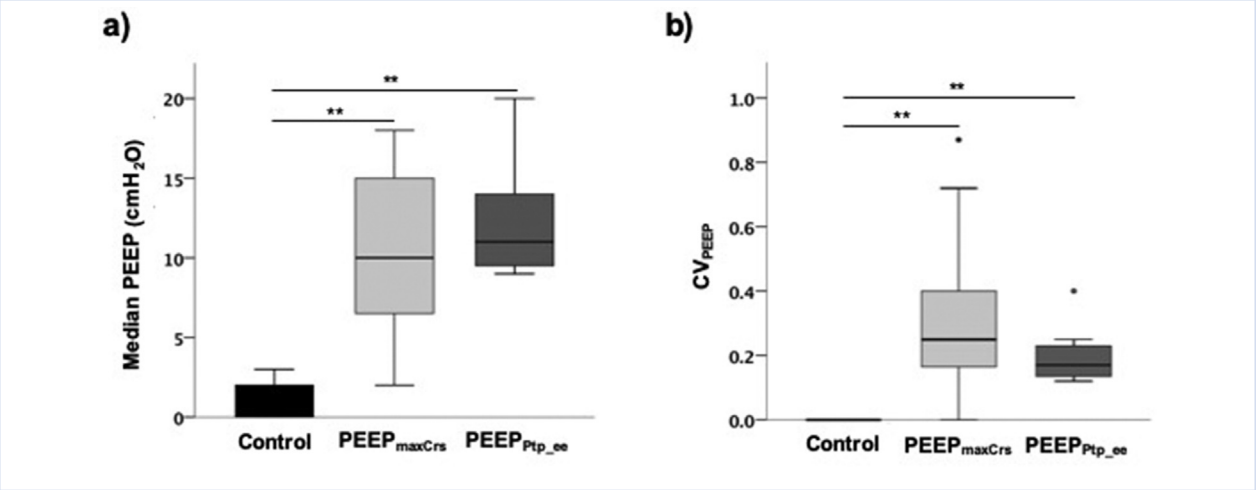

Fig 2. PEEP variability. (a) Variability of median PEEP levels between patients receiving a constant PEEP ≤2 cm H_2O (control) or individualised PEEP ($PEEP_{maxCrs}$ or $PEEP_{Ptp\_ee}$); and (b) variability of PEEP levels within patients throughout surgery measured by the PEEP coefficient of variation (CV_{PEEP}) for all PEEP levels used for each individual. (**$P \leq 0.01667$ in *post hoc* comparison of respective group compared with control).

≤0.0125 (=0.05/4) was used; otherwise 0.05 was used for overall statistical tests. For *post hoc* pairwise comparisons amongst the three groups after the overall test was found to be statistically significant, a significance level of <0.01667 (=0.05/3) was used.

Sample size estimation

This study was designed to include 40 subjects (minimum 13 per group) from all sites to select the individualised PEEP method that reduces intraoperative ΔP. A sample size of 13 subjects per group was estimated to have 80% power to detect a clinically relevant difference of 4 cm H_2O in ΔP between the three groups, assuming a standard deviation of 3.6 cm H_2O based on preliminary results from a recent publication[31] (α=0.05, two-sided, analysis of variance). Our sample size estimation allowed for potential drop-outs before surgery and to adjust for the potential loss of power using a non-parametric test.

Results

Subject characteristics

Forty-six subjects were enrolled and randomised (Fig. 1). Six patients never received the assigned intervention; three participants failed to complete the $PEEP_{Ptp\_ee}$ intervention because of surgical complications (n=1) or inability to measure P_{es} (n=2). There were no protocol deviations in subjects from the $PEEP_{maxCrs}$ and control groups. Thus, 37 subjects were included in the final analysis (Fig. 1) comprising 13 controls, 16 $PEEP_{maxCrs}$, and eight $PEEP_{Ptp\_ee}$ subjects. Perioperative details were similar between each group (Tables 1 and 2, Supplementary Tables S1 and S2). Peak and plateau airway pressures and $P_{ET}CO_2$ were significantly higher in the $PEEP_{Ptp\_ee}$ group than controls (Table 2). Individualised PEEP was associated with higher heart rate for both $PEEP_{maxCrs}$ and $PEEP_{Ptp\_ee}$ groups (Table 2).

Primary (composite) outcomes

All four of the primary outcomes were different between the three groups (each p<0.0125) (Table 2):

(1) Intraoperative ΔP: subjects randomised to $PEEP_{maxCrs}$ and $PEEP_{Ptp\_ee}$ had lower intraoperative ΔP and higher C_{rs} compared with controls (Table 2).
(2) P_{tp_ee}: median values for P_{tp_ee} were higher in both PEEP individualisation groups, compared with controls (Table 2). A P_{tp_ee}>0 cm H_2O was achieved following all PEEP titrations in the $PEEP_{Ptp\_ee}$ group and in 78 (49–96)% of the $PEEP_{maxCrs}$ titrations.
(3) C_{rs}: maintained or increased C_{rs} was achieved in 80 (64–100)% after PEEP interventions in the $PEEP_{maxCrs}$ group. C_{rs} was maintained or increased in 73 (62–92)% of the interventions undertaken in the $PEEP_{Ptp\_ee}$ group.
(4) PEEP values: In both $PEEP_{maxCrs}$ and $PEEP_{Ptp\_ee}$ groups, median PEEP levels were higher than those in controls (Table 2). The intraoperative individualised PEEP ranged from 2 to 20 cm H_2O (median:10 cm H_2O [8–15]) for combined individualised PEEP groups; Table 2; Fig. 2a). The CV_{PEEP} in the intervention PEEP groups ranged from 0 to 0.87 (median: 0.24 [0.14–0.35]; Table 2; Fig. 2b).

Secondary outcomes

Measures of respiratory mechanics

P_{es_ee} and other respiratory mechanic measurements were similar in both PEEP individualisation groups (Table 2). End-inspiratory respiratory parameters (P_{es_ei}, P_{tp_ei}) were also similar between each group (Fig. 3, Supplementary Table 3). We observed a significant correlation between airway and transpulmonary driving pressures (R^2=0.801, P<0.001; Fig. 3) and between respiratory system and lung elastance (R^2=0.748, P<0.001; Fig. 3).

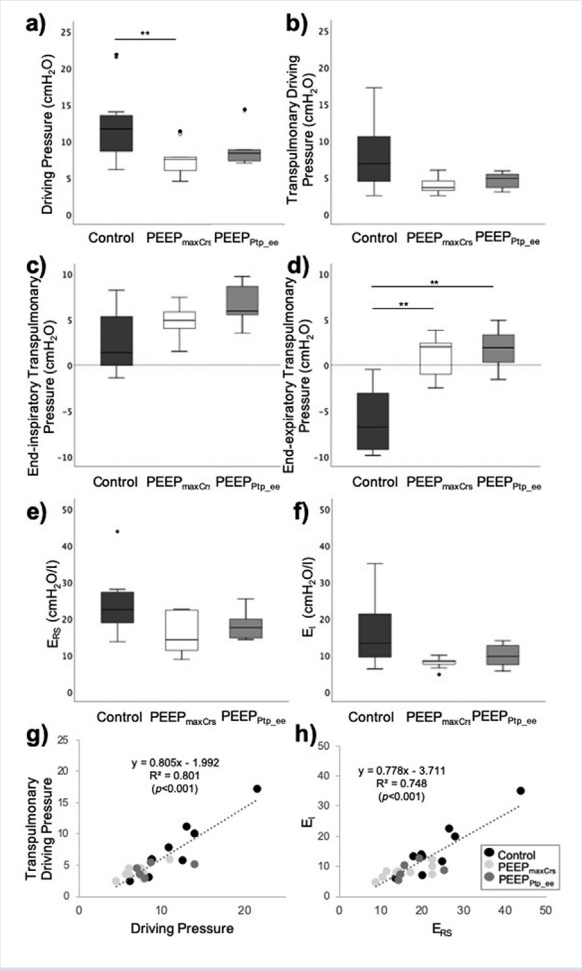

Fig 3. Intraoperative respiratory parameters in a subgroup of subjects with end-inspiratory P_{es} measurements. (a) Driving pressure. (b) Transpulmonary driving pressure. (c) End-inspiratory transpulmonary driving pressure. (d) End-expiratory transpulmonary driving pressure. (e) Respiratory system elastance (E_{RS}). (f) Lung elastance (E_L). (g) Correlation between driving pressure and transpulmonary driving pressure. (h) Correlation between respiratory system elastance (E_{rs}) and lung elastance (E_L). (Boxplots represent median (Q1, Q3); error bars represent minimum and maximum values; full dots identify outlier values. Results of *post hoc* comparisons are shown if significant differences observed between the three groups: for *post hoc* comparisons, $P \leq 0.01667$ (=0.05/3) statistically significant. However, we also indicate for completeness all two-group comparisons where $0.01667 < P < 0.05$ as these would be considered significant if we had not adjusted for multiple comparisons. *P-value $0.01667 < P < 0.05$ compared with control; ^P-value $0.01667 < P < 0.05$ $PEEP_{Ptp\_ee}$ *vs* $PEEP_{maxCrs}$ **$P \leq 0.01667$ compared with control; ^^$P \leq 0.01667$ $PEEP_{Ptp\_ee}$ *vs* $PEEP_{maxCrs}$.).

Plasma lung injury biomarkers and clinical morbidity

Absolute plasma levels of lung injury biomarkers were similar across groups (Fig. 4). Ratiometric measures of the epithelial injury biomarkers CC16 and sRAGE levels were lower in both PEEP-individualisation groups, compared with controls. $PEEP_{maxCrs}$ subjects had higher T_{24h}/T_0 ratios for the endothelial injury biomarker Ang-2, compared with controls. Subjects randomised to $PEEP_{Ptp\_ee}$ had higher PAI-1 T_{24h}/T_0 ratios compared with controls (Supplementary Table 4). Postoperative pulmonary complications were minor and similar between groups (Supplementary Table 5).

Discussion

This prospective randomised multicentre pilot study suggests that periodic individualised PEEP aiming at optimising either intraoperative C_{rs} or P_{tp_ee} during abdominal surgery results in reduced ΔP, increased C_{rs} and maintains positive P_{tp_ee}, compared with a constant PEEP≤2 cm H_2O. These interventions resulted in widely variable PEEP levels both between and within subjects throughout surgery.

Data on the optimal approach to set intraoperative PEEP are controversial.[5,8,11,14] Our pilot results show that periodically optimising PEEP with two bedside interventions effectively reduced ΔP throughout abdominal surgery. Such a finding has physiological and clinical relevance. Physiologically, it reflects a reduction in cyclic lung strain[32,33] likely because of an optimised balance between lung overdistension and derecruitment.[26] Indeed, a recent study using electrical impedance tomography to individualise PEEP at the onset of abdominal surgery resulted in values similar to those in our intervention patients (~10 cm H_2O).[15] Clinically, reduced ΔP may limit major PPCs including acute respiratory distress syndrome (ARDS), pneumonia, pulmonary oedema, need for reintubation, pulmonary infection, and barotrauma.[12,34]

PEEP adjustments required to achieve the low ΔP varied substantially between and within patients throughout abdominal surgery. Data on intraoperative variability of respiratory system mechanics are rarely available. The observed range of interindividual optimised median PEEP was 2–20 cm H_2O. Consequently, based on this individualised PEEP range, had we used a constant PEEP=12 cm H_2O in all our intervention patients (as in the PROtective Ventilation using HIgh vs. LOw PEEP, PROVHILO, study)[7] we would have overdistended 67% (16/24) of the lungs as their individualised PEEP was <12 cm H_2O, and under-recruited 33% (eight of 24) with individualised PEEP>12 cm H_2O. The variability of individualised PEEP was also notable within patients, ranging from 0% to 87%. This finding emphasises the relevance of individualising PEEP settings *throughout surgery*, a concept often not considered in studies pursuing individualised PEEP. For example, both in a recent imaging-guided PEEP trial[15] and in a major clinical trial[35] including PEEP-individualisation, PEEP was titrated only once at the beginning of surgery and that PEEP was maintained unchanged until extubation. Our results clearly show that a constant PEEP, even if individualised to optimise respiratory system mechanics at the onset of surgery, is not sufficient to maintain such optimisation throughout the dynamic conditions of abdominal surgery. Our finding of large intra- and interindividual variabilities of individualised PEEP settings strongly supports this point.

Maintaining a positive P_{tp_ee} during mechanical ventilation aims to avoid atelectasis by ensuring end-expiratory alveolar pressures greater than pleural pressures (or their surrogate P_{es}).[27,36] This method has been previously applied in patients with ARDS and shown to increase oxygenation and C_{rs}.[16] Of note, P_{tp_ee} was positive at most intervention time points while all controls presented negative P_{tp_ee}, suggesting that individualised PEEP resulted in less end-expiratory lung derecruitment. There is considerable controversy on the

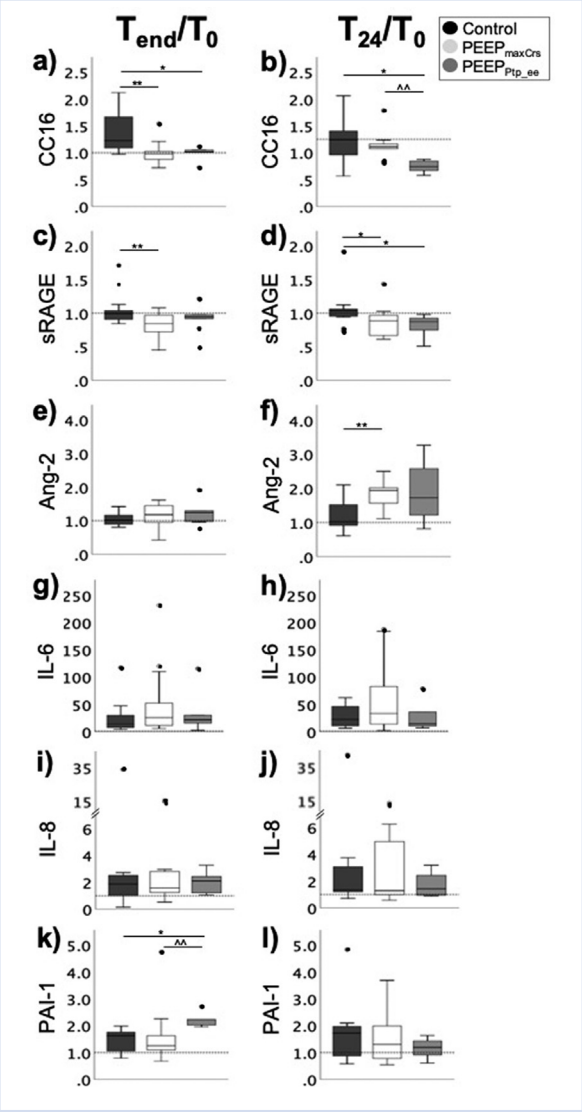

Fig 4. Plasma concentrations of biomarkers of lung injury. Ratios of plasma concentrations of biomarkers of: epithelial injury (club cell protein-16 [CC16] and soluble form of the receptor for advanced glycation end-products [sRAGE]) (a–d); endothelial injury (angiopoietin-2 [Ang-2]) (e–f); inflammation (interleukin [IL]-6 and IL-8) (g–h); and endothelial-derived coagulation activation (plasminogen activator inhibitor-1 [PAI-1]) (i–j) at the end of (T_{end}) and after 24 h (T_{24}) compared with baseline (T_0). (Boxplots represent median (Q1, Q3); error bars represent minimum and maximum values; full dots identify outlier values. Results of *post hoc* comparisons are shown if significant differences observed between the three groups: for *post hoc* comparisons, *P*-values≤ 0.01667 (=0.05/3) statistically significant. However, we also indicate for completeness all two-group comparisons where 0.01667<*P*<0.05 as these would be considered significant if we had not adjusted for multiple comparisons. **P*-value 0.01667<*P*<0.05 compared with control; ^*P*-value 0.01667<*P*<0.05 $PEEP_{Ptp\_ee}$ *vs* $PEEP_{maxCrs}$; **$P \leq 0.01667$ compared with control; ^^$P \leq 0.01667$ $PEEP_{Ptp\_ee}$ *vs* $PEEP_{maxCrs}$.).

approach to set PEEP for a positive P_{tp_ee}.[27,36–38] The P_{tp_ee} method presumes equality between absolute pleural pressure and P_{es}. This presumption has been criticised because: (a) P_{tp_ee} is negative in several conditions, as in our controls, leading to an expected substantially-collapsed lung,[39,40] which is inconsistent with simultaneous physiological observations; (b) absolute P_{es} did not correlate with CT-derived lung weight in ARDS[38]; (c) the use of P_{tp_ee} to set PEEP resulted in levels neither related to lung recruitability[38] nor to ARDS severity.[37] An alternative to select PEEP proposes elastance ratios (E_L/E_{rs}).[41] P_{tp} computed with this method represents that existing in the non-dependent lung at risk for excessive strain.[17] However, this elastance-based approach has also been criticised for the assumption of zero pleural pressure at relaxed functional residual capacity (FRC) with zero PEEP.[42,43] Of note, our elastance ratios (E_L/E_{rs}) and elastance-derived P_{tp} were within normal ranges (Fig. 3, Supplementary Table S3),[17,41] consistent with healthy lungs. We used absolute P_{es_ee} measurements based on recent use[16] and on findings in lung-injured pigs and human cadavers[17] indicating that they reflect pleural pressures in the dependent-to-middle lung regions, that is those most susceptible to atelectasis. It should be emphasised that P_{tp_ee} is a local measure, not representative of the whole lung. We speculate that this partially explains why our controls with negative P_{tp_ee} were not significantly hypoxaemic, as the distribution of non-aerated lung is larger in the dorso-subdiaphragmatic areas where the oesophageal balloon is positioned. The remaining volume of ventilated lung together with a normal hypoxic pulmonary vasoconstriction would have contributed to maintenance of oxygenation.

We found that P_{es} monitoring can present technical challenges during dynamic surgical conditions but, when available, the $PEEP_{Ptp\_ee}$ method is similarly effective to $PEEP_{maxCrs}$ in reducing ΔP. The strong correlations between airway and transpulmonary driving pressures, and between respiratory system and lung elastance (Fig. 3) support the use of the clinically available measures (airway ΔP, E_{RS}) as acceptable surrogates of more complex and P_{es}-dependent measures (transpulmonary driving pressures, E_L) in surgical patients.

Our baseline plasma biomarker measurements were comparable to previous findings.[20] $PEEP_{maxCrs}$ titration reduced epithelial injury biomarkers CC-16 and sRAGE by the end of surgery (T_{end}/T_0). Interestingly, levels of these markers on postoperative day 1 relative to baseline increased in patients receiving PEEP=12 cm H_2O compared with PEEP≤2 cm H_2O in the PROVHILO trial.[20] Such contrasting results could reflect overdistention-related injury induced by a fixed-high PEEP rather than epithelial protection achieved with an individualised-high PEEP in our study. Further investigation will be needed to confirm our observed increased plasma biomarkers of endothelial injury Ang-2 in $PEEP_{maxCrs}$ (T_{24h}/T_0) and coagulation activation PAI-1 in the $PEEP_{Ptp\_ee}$ (T_{end}/T_0) compared with controls.

There were several major limitations in this study, with six subjects being excluded before receiving any intervention. Although the reasons (mostly surgery being rescheduled/cancelled) were beyond the control of the investigators, a possible selection bias cannot be excluded. The uneven distribution of excluded subjects within the groups reduced the power to detect differential effects in the $PEEP_{Ptp\_ee}$ group. Radiological evaluations were not mandatory, and thus

positive postoperative findings of atelectasis or pleural effusion may have been affected by selection bias. This study was designed to test the impact of two individualised PEEP methods during abdominal surgery on respiratory system mechanics. It was not powered to detect differences on end-inspiratory P_{es}, biomarker levels, clinical outcomes, or between open *vs* laparoscopic surgery. Recent findings[11] suggest that ΔP during abdominal surgery reflects global dynamic lung strain only when PEEP results in aerated lung volumes below the FRC. However, the relationship between ΔP and PPCs has been established in large studies for a broad range of PEEP settings.[12,13,34] This supports our use of ΔP and suggests that additional factors such as the regional magnitude and interplay of static and dynamic strains[44] could relate to lung injury. Repeated PEEP titrations cannot be recommended until demonstration of improved clinical outcomes, particularly considering unclear results of recent PEEP studies.[14,45] We did not observe any hypotension during PEEP titration that impeded the implementation of the protocol. However, the slightly higher intraoperative HR, larger volume of administered albumin, and trend to larger phenylephrine use in the individualised PEEP groups warrant examination of the haemodynamic consequences of individualisation approaches in a larger study.

We conclude that periodic individualised PEEP targeting optimised respiratory system mechanics during abdominal surgery results in reduced ΔP, maintains positive P_{tp_ee} and increases C_{rs} by using PEEP levels that vary widely between and within subjects during surgery, compared with a constant PEEP≤2 cm H_2O. The C_{rs}-guided PEEP optimisation seems preferable for intraoperative PEEP titration owing to the simplicity of implementation. Individualised PEEP reduced intraoperative ΔP and improved respiratory system mechanics without significant hypotension or other adverse events. The wide variability of optimised PEEP levels observed between subjects and during abdominal surgery suggest that a 'one-size-fits-all' intraoperative PEEP strategy should not be a standard of care. However, larger trials to assess clinically relevant outcomes are needed before periodic individualised PEEP can be recommended.

Authors' contributions

Study conception: AFB, JS, BTT, MFVM
Study performance: AFB, JS, KB, TW, CK, MFVM
Data collection: AFB, JS, KB, TW, CK, MFVM
Data analysis and interpretation: AFB, RAP, MFVM
Manuscript preparation: AFB, RAP, MFVM
Approval of the final version of the manuscript: JS, KB, TW, CK, BTT

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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