ANESTHESIOLOGY

Intraabdominal Pressure Targeted Positive End-expiratory Pressure during Laparoscopic Surgery

An Open-label, Nonrandomized, Crossover, Clinical Trial

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ABSTRACT

Background: Pneumoperitoneum for laparoscopic surgery is associated with a rise of driving pressure. The authors aimed to assess the effects of positive end-expiratory pressure (PEEP) on driving pressure at varying intraabdominal pressure levels. It was hypothesized that PEEP attenuates pneumoperitoneum-related rises in driving pressure.

Methods: Open-label, nonrandomized, crossover, clinical trial in patients undergoing laparoscopic cholecystectomy. “Targeted PEEP” (2 cm H_2O above intraabdominal pressure) was compared with “standard PEEP” (5 cm H_2O), with respect to the transpulmonary and respiratory system driving pressure at three predefined intraabdominal pressure levels, and each patient was ventilated with two levels of PEEP at the three intraabdominal pressure levels in the same sequence. The primary outcome was the difference in transpulmonary driving pressure between targeted PEEP and standard PEEP at the three levels of intraabdominal pressure.

Results: Thirty patients were included and analyzed. Targeted PEEP was 10, 14, and 17 cm H_2O at intraabdominal pressure of 8, 12, and 15 mmHg, respectively. Compared to standard PEEP, targeted PEEP resulted in lower median transpulmonary driving pressure at intraabdominal pressure of 8 mmHg (7 [5 to 8] *vs.* 9 [7 to 11] cm H_2O; $P = 0.010$; difference 2 [95% CI 0.5 to 4 cm H_2O]); 12 mmHg (7 [4 to 9] *vs.*10 [7 to 12] cm H_2O; $P = 0.002$; difference 3 [1 to 5] cm H_2O); and 15 mmHg (7 [6 to 9] *vs.*12 [8 to 15] cm H_2O; $P < 0.001$; difference 4 [2 to 6] cm H_2O). The effects of targeted PEEP compared to standard PEEP on respiratory system driving pressure were comparable to the effects on transpulmonary driving pressure, though respiratory system driving pressure was higher than transpulmonary driving pressure at all intraabdominal pressure levels.

Conclusions: Transpulmonary driving pressure rises with an increase in intraabdominal pressure, an effect that can be counterbalanced by targeted PEEP. Future studies have to elucidate which combination of PEEP and intraabdominal pressure is best in term of clinical outcomes.

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EDITOR’S PERSPECTIVE

What We Already Know about This Topic

- Transpulmonary driving pressure (ratio of tidal volume to respiratory system compliance) increases with increased intraabdominal pressure during laparoscopic surgery. High transpulmonary driving pressure during laparoscopic surgery is associated with increased risk of postoperative pulmonary complications.
- Intraoperative positive end-expiratory pressure prevents atelectasis, but may also cause overdistension.

What This Article Tells Us That Is New

- This single-center study found that titrating intraoperative positive end-expiratory pressure in relation to observed intraabdominal pressure may counterbalance pneumoperitoneum-related rises in transpulmonary driving pressure during laparoscopic cholecystectomies.

The intraoperative driving pressure, the ratio of tidal volume (V_T) to respiratory system compliance, reflects the strain applied on lung tissue in patients receiving ventilation during general anesthesia for surgery.[1] Driving pressure depends on the amounts of atelectatic and overdistended lung tissue during intraoperative ventilation.[2] Since a rise in intraoperative driving pressure—irrespective of its cause—increases the risk of postoperative pulmonary

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complications,[3] strategies aimed at preventing a rise in driving pressure may benefit surgery patients.[4]

In patients undergoing laparoscopic abdominal surgery, intraoperative driving pressure rises because of several reasons other than those described previously, and to a greater extent than with nonlaparoscopic surgery: (1) the chest wall becomes stiffer during peritoneum insufflation, causing a rise of the respiratory system driving pressure (this may not necessarily mean that the transpulmonary driving pressure rises equally)[5–12]; (2) the cranial shift of the diaphragm with pneumoperitoneum strongly favors the formation of atelectases[13,14]; and (3) intraoperative ventilation with low V_T, by now a standard preventive measure against the development of postoperative pulmonary complications,[11,12,15] could further favor the formation of atelectases during peritoneum insufflation.[16]

Individualized positive end-expiratory pressure (PEEP) titration has been shown to prevent rises in transpulmonary and respiratory system driving pressure during pneumoperitoneum,[5–8] as it may counterbalance the atelectasis-inducing effects of the cranial shift of the diaphragm, mainly with use of low V_T.[7,11] However, PEEP could also cause a rise in driving pressure when it results in overdistension of the nondependent lung parts.[17] The current clinical trial in patients undergoing laparoscopic cholecystectomy was conducted to determine the feasibility of PEEP titrated to the intraoperative abdominal pressure levels to lower transpulmonary driving pressure. It was hypothesized that higher PEEP, targeting the intraabdominal pressure, prevents a rise in transpulmonary driving pressure during intraoperative ventilation with pneumoperitoneum.

Materials and Methods

Study Design

This was an open-label, prospective, nonrandomized, crossover, single-center clinical trial performed at the University and Polytechnic Hospital la Fe in Valencia, Spain. The Institutional Review Board of the hospital approved the investigational protocol (protocol no. 2016/0602), and the trial was compliant with the Helsinki Declaration. Written informed consent was obtained from all subjects before entering the trial. The trial was registered at www.clinicaltrials.gov (study identifier: NCT03435913). Full access to the protocol is available by request.

Inclusion and Exclusion Criteria

Patients were approached by study staff and were eligible if they: (1) were aged 18 yr or older; (2) had an American Society of Anesthesiology (Schaumburg, Illinois) Physical Status score of less than IV; and (3) planned for laparoscopic cholecystectomy. Exclusion criteria included: (1) pregnancy or breastfeeding; or (2) advanced renal, hepatic, or cardiopulmonary disease.

Anesthesia and Pneumoperitoneum Induction and Maintenance

All patients were monitored continuously using electrocardiography, noninvasive blood pressure registration, pulse oximetry and capnography, respiratory gas analysis (Carescape; GE Healthcare, USA), and Bispectral Index monitoring (Covidien, Ireland). General anesthesia was induced with propofol, and maintained with either desflurane or sevoflurane (targeting a Bispectral Index value between 40 and 60) and remifentanil, through continuous intravenous infusion with fentanyl boluses as required. An upper body forced-air warming blanket (Bair Hugger; 3M, USA) was used to maintain normothermia.

Kinemyography was performed by placing sensors on the thenar eminence of the hand to assess neuromuscular block (NMT Mechanosensor, GE Healthcare). Patients received deep neuromuscular blockade throughout ventilation to maintain a train-of-four of 0 and a posttetanic count between 1 and 5.

Ventilator settings were set as follows: V_T of 7 ml/kg of predicted body weight; respiratory rate of 12 breaths/min; inspiration to expiration ratio of 1:2; and inspiratory pause of 20% of the total inspiratory time.

Pneumoperitoneum was created by initially setting the carbon dioxide gas insufflator (Endoflator; Karl Storz, Germany) to achieve a pressure of 15 mmHg with a flow rate of 1.5 l/min and performing insertion of trocars. Subsequently, the patient was placed in the surgical position (20-degrees anti-Trendelenburg).

Esophageal Probe Placement and Pressure Monitoring

A balloon-tipped latex esophageal probe (MBMed BA-A-008; MBMED, Argentina) was inserted through the mouth and advanced approximately 55 to 60 cm. According to the manufacturer's recommendations, the balloon was filled with 1.5 ml of air, the top value of the manufacturer's recommended range, after which the intragastric position was checked by observing a pressure deflection with gentle external manual epigastric pressure. The catheter was then withdrawn into the esophagus. Subsequently, the positioning in the lower third was checked by assessing heart artifacts and by performing the expiratory occlusion test as previously described.[18] The catheter was considered properly placed if, during the test, esophageal pressure changes were related to changes in airway pressure within a ratio range of 0.9 to 1.1. The catheter was then connected to a pressure monitor (FluxMed GrE; MBMED) to measure the esophagus pressure.

Study Interventions and Measurements

Study interventions and measurements were performed in the time window between stable pneumoperitoneum and start of the surgical procedure, typically lasting 20 to 30 min. During this period, the patient was left untouched by the anesthesiologists and surgeons. Due to this pragmatic setting, blinding of healthcare providers was not feasible.

At three different predetermined intraabdominal pressure levels, PEEP was set at 5 cm H_2O (“standard PEEP”) for 2 min, and after that at 2 cm H_2O above intraabdominal pressure (“targeted PEEP,” where 1 mmHg intraabdominal pressure = 1.36 cm H_2O) for 2 min. Every protocol-dictated change in PEEP and intraabdominal pressure was preceded by a standard recruitment maneuver as previously described,[19] and detailed in the Methods section (http://links.lww.com/ALN/C183) and in figure 1 (http://links.lww.com/ALN/C184) of the Supplemental Digital Content. With each new step in the study protocol, PEEP was reduced to 5 cm H_2O and a recruitment maneuver was repeated so that we returned to baseline pulmonary conditions as much as possible. To achieve the three predefined intraabdominal pressure levels, the flow rate at the carbon dioxide gas insufflator was increased to 30 l/min, and intraabdominal pressure was first lowered to 8 mmHg, then increased to 12 mmHg, and finally to 15 mmHg. Each patient was subjected to every intraabdominal pressure step in a strict sequence before the start of the surgical intervention.

At baseline before pneumoperitoneum, and 2 min after each PEEP adjustment, airway and esophagus pressure measurements were performed to obtain the plateau pressure, the peak inspiratory pressure, the end-inspiratory esophageal pressure, and the end-expiratory esophageal pressure. After the last measurement, PEEP and intraabdominal pressure were set following surgical team clinical criteria and surgery started. For details, see the Methods section (http://links.lww.com/ALN/C183) and figure 1 (http://links.lww.com/ALN/C184) in the Supplemental Digital Content.

Data Collection

Patient height, weight, body mass index, gender, American Society of Anesthesiologists Physical Status, number of previous abdominal surgeries, number of previous pregnancies, and respiratory comorbidities were recorded before surgery. In addition, the following parameters were calculated as follows: respiratory system driving pressure = plateau pressure − PEEP; end-inspiratory pulmonary pressure = plateau pressure − end-inspiratory esophageal pressure; end-expiratory pulmonary pressure = end-expiratory airway pressure (defined as PEEP during expiratory hold) − end-expiratory esophageal pressure; transpulmonary driving pressure = end-inspiratory pulmonary pressure − end-expiratory pulmonary pressure; respiratory system compliance = V_T/(plateau pressure − PEEP); chest wall compliance = V_T/(end-inspiratory esophageal pressure − end-expiratory esophageal pressure); and pulmonary compliance = V_T/ transpulmonary driving pressure. We measured plateau pressure by using an end-inspiratory occlusion of 0.5 s. Hemodynamic instability was defined as any episodes of hypotension with systolic arterial pressure less than 90 mmHg for 3 min or longer. Blood pressure was monitored during all study-related interventions, including recruitment maneuvers.

Study Endpoints

The primary endpoint was the difference in transpulmonary driving pressure between targeted PEEP and standard PEEP at the three predefined intraabdominal pressure levels. Secondary endpoints included the relationship between respiratory system driving pressure and transpulmonary driving pressure, and the difference in respiratory system driving pressure between targeted PEEP and standard PEEP at the three predefined intraabdominal pressure levels. No interim analyses or rules for early stopping of the trial were included in the study protocol.

Sample Size Calculation

Comparable studies have been carried out in animal models of abdominal hypertension, but in those studies, neuromuscular blockage agents were not used. Therefore, the assumptions for the sample size calculation were built upon findings in clinical investigations.[21,22] Based on respiratory system driving pressure measurements in those studies and the assumption that transpulmonary driving pressure would drop from 18 ± 6 cm H_2O to below a safer level of 13 cm H_2O with PEEP matching, we calculated that 25 patients would be needed to have a power of 90% and an α error of 0.05 for a two-tailed hypothesis test. To compensate for dropouts due to potential problems while placing or using the esophagus pressure catheter, 30 patients were included (fig. 2 in the Supplemental Digital Content, http://links.lww.com/ALN/C185).

Statistical Analysis

Data are presented as proportions and percentages or medians (with 25th to 75th percentiles) where appropriate. Normality of distributions was assessed by inspection of quantile–quantile plots. Logarithmic transformation of variables for regression model fitting was performed for nonnormally distributed variables. Differences in medians were assessed with a Wilcoxon rank sum test.

First, transpulmonary driving pressure was compared at the three intraabdominal pressure levels between targeted PEEP and standard PEEP. For this, a mixed-effect linear regression model was used with the following prespecified features: transpulmonary driving pressure as the dependent variable and PEEP level (targeted and standard) as fixed effect; individuals were introduced as a random factor with a random intercept. Intraabdominal pressure level (as an ordinal categorical variable with three levels), body mass index, and baseline transpulmonary driving pressure before peritoneum were introduced as covariables. Moreover, an interaction term between intraabdominal pressure level and PEEP level were also included in the model. Also, a similar mixed-effect linear regression model was used with respiratory system driving pressure as the dependent variable. Covariables' adjustment were prespecified in the analysis plan. No stratification analysis was performed.

Second, the relationship between transpulmonary driving pressure and respiratory system driving pressure was determined by Pearson correlation coefficient and local polynomial regression.

In a *post hoc* analysis, Bayesian mixed-effect modeling was performed with intraabdominal pressure as a monotonic effect. These models were built to evaluate the effect of simulating stepwise behavior in the variable at every 1 mmHg of intraabdominal pressure on the relationship between PEEP regime and transpulmonary driving pressure, and respiratory system driving pressure with the same covariable structure of the mixed-effect models previously discussed. For this analysis, we used the R package *brms* which implements mixed-effects models estimation with Hamiltonian Markov No U-turn sampler setting the previous distribution with the default from the package to have a weak prior with small influence (half Student *t* prior with 3 degrees of freedom, location of 0 and scale of 10).

All analyses were repeated for lung compliance and respiratory system compliance and reported in the Supplemental Digital Content.

All statistical analyses were performed with Stata (Statacorp, USA) and R 3.5.1 (The R Foundation for Statistical Computing, https://www.r-project.org). Statistical significance was set for two-tailed at $P < 0.05$.

Results

Patients

In total, 30 patients were included in this study between April 2018 and November 2018. Patients' demographics and ventilation characteristics are presented in table 1. The study protocol was strictly followed and completed in all patients, without episodes of hemodynamic instability in the time window of intraabdominal pressure and PEEP titrations for this study. There were no missing data. The trial was conducted and finished in accordance to the study protocol.

Effect of Targeted PEEP on Transpulmonary and Respiratory System Driving Pressure at Three Intraabdominal Pressure Levels

Transpulmonary and respiratory system driving pressure for standard PEEP and targeted PEEP at the three predefined intraabdominal pressure levels are presented in figure 1 and table 2. For standard PEEP, median transpulmonary driving pressure at intraabdominal pressure of 15 mmHg was higher compared to median transpulmonary driving pressure at intraabdominal pressure of 12 mmHg or 8 mmHg. Targeted PEEP resulted in a lower median transpulmonary driving pressure at all three intraabdominal pressure levels compared to standard PEEP. As shown in tables 1 (http://links.lww.com/ALN/C186) and 2 (http://links.lww.com/ALN/C187) in the Supplemental Digital Content, Transpulmonary and respiratory system driving pressure were lower for targeted PEEP when compared to standard PEEP, after controlling for several confounders and individual variability.

Table 1. Baseline Characteristics

Age, yr	60 [57–74]
Gender, female	19 (63.3)
Weight, kg	72 [65–83]
Height, cm	161 [156–166]
ASA	
I	2 (6.7)
II	20 (66.7)
III	8 (26.7)
Previous respiratory disease, yes	4 (13.3)
No. of previous pregnancies	
0	14 (46.7)
1	3 (10.0)
2	8 (26.7)
3	4 (13.3)
7	1 (3.3)
No. of previous open surgeries	
0	15 (50.0)
1	7 (23.3)
2	7 (23.3)
3	1 (3.3)
Number of previous laparoscopic surgeries	
0	28 (93.3)
1	1 (3.3)
2	1 (3.3)
Tracheal tube internal diameter, mm	8 [8–8]
Intraabdominal volume at 15 cm H_2O at first insufflation, l	5 [4–5]
Body mass index, kg/m^2	27 [25–30]
Predicted body weight, kg	54 [49–61]
V_T, ml	400 [400–450]
Respiratory peak pressure, cm H_2O	20 [17–24]
Respiratory plateau pressure	16 [14–20]
End-inspiratory esophageal pressure	14 [9–19]
End-expiratory esophageal pressure	10 [6–15]
Respiratory driving pressure	10 [9–15]
Transpulmonary driving pressure	8 [5–12]
Respiratory system compliance, ml/cm H_2O	38 [27–48]
Chest wall compliance, ml/cm H_2O	124 [100–200]
Lung compliance, ml/cm H_2O	55 [33–85]

Data are reported as number (%) or median [25th to 75th percentile]. ASA, American Society of Anesthesiologists physical status; V_T, tidal volume.

Relationship between Transpulmonary and Respiratory System Driving Pressure

Transpulmonary and respiratory system driving pressure showed a moderate-to-strong linear relationship (fig. 2) and a strong correlation. Table 3 presents transpulmonary and respiratory system driving pressure correlation by intraabdominal pressure level. The correlation between transpulmonary and respiratory system driving pressure decreased at intraabdominal pressure of 12 mmHg and intraabdominal pressure of 15 mmHg, compared to the decrease at intraabdominal pressure of 8 mmHg, but remained moderate-to-strong. The full correlation matrix is showed

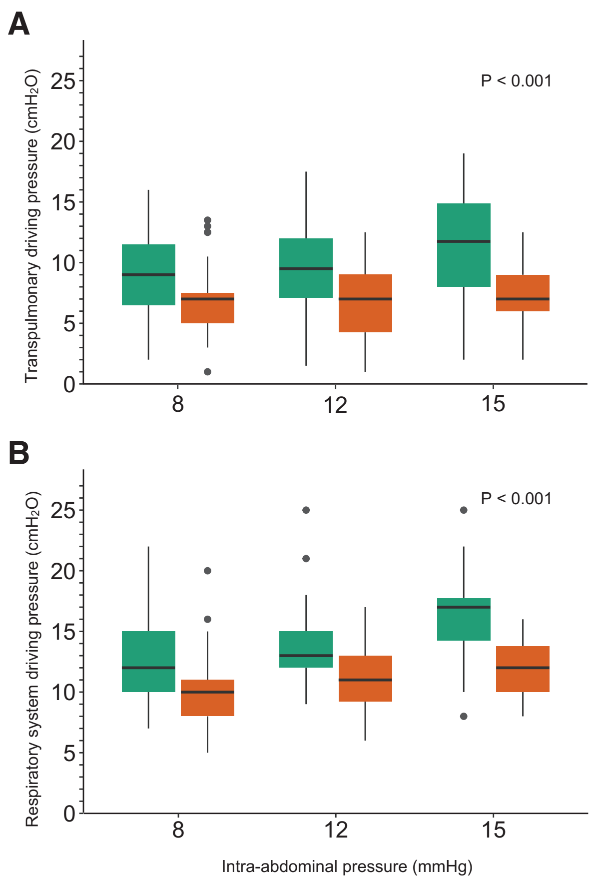

Fig. 1. Boxplots for transpulmonary and respiratory system driving pressures by intraabdominal pressure level at "standard PEEP" and "targeted PEEP." (*A*) Transpulmonary driving pressure, (*B*) respiratory system driving pressure. *Green boxes* represent the standard PEEP group, *orange boxes,* the targeted PEEP group. *P* values reported are from the multivariable analysis. Transpulmonary and respiratory system driving pressures are reported in cm H_20 and intraabdominal pressure in mmHg. PEEP, positive end–expiratory pressure.

in figures 3 to 5 in the Supplemental Digital Content (http://links.lww.com/ALN/C188, http://links.lww.com/ALN/C189, and http://links.lww.com/ALN/C190).

Effect of Targeted PEEP on Respiratory System, Lung, and Chest Wall Compliance

For standard PEEP, median lung compliance at an intraabdominal pressure of 15 mmHg was lower compared to median lung compliance at an intraabdominal pressure of 8 mmHg or 12 mmHg. Likewise, targeted PEEP increased median lung compliance compared to standard PEEP at all three intraabdominal pressure levels. While targeted PEEP significantly increased respiratory system compliance at all three intraabdominal pressure levels, chest wall compliance had no relationship in the univariate analysis. Multivariable regression showed that lung compliance decreased at standard PEEP when compared to targeted PEEP. (Supplemental Digital Content, table 3 [http://links.lww.com/ALN/C191], table 4 [http://links.lww.com/ALN/C192], fig. 6 [http://links.lww.com/ALN/C193] and fig. 7 [http://links.lww.com/ALN/C194]).

Effect of Targeted PEEP on Pulmonary and Esophageal Pressure

With targeted PEEP end-inspiratory pulmonary pressure was higher at all three intraabdominal pressure level with an increasing difference with increasing intraabdominal pressure levels. Similarly, end-expiratory pulmonary pressure was higher with targeted PEEP, and at standard PEEP the median end-expiratory pulmonary pressure was negative (table 2).

Post Hoc Analysis

The results of the *post hoc* analysis are presented in figure 3, and in figure 7 (http://links.lww.com/ALN/C194), and table 5 (http://links.lww.com/ALN/C195), table 6 (http://links.lww.com/ALN/C196) and table 7 (http://links.lww.com/ALN/C197) in the Supplemental Digital Content. Intraabdominal pressure had a significant monotonic effect with higher intraabdominal pressures associated with higher transpulmonary and respiratory system driving pressure, with a larger effect at intraabdominal pressure greater than 12 mmHg and a posterior probability greater than 0.999. Moreover, targeted PEEP reduced transpulmonary driving pressure by 2.41 (95% credibility interval, 1.45 to 3.34) cm H_2O compared to standard PEEP with a posterior probability greater than 0.999. The model estimated that the difference in transpulmonary driving pressure between 8 and 15 mmHg for intraabdominal pressure was 1.83 (95% CI, 0.82 to 2.86) cmH_2O (Supplemental Digital Content table 5A, http://links.lww.com/ALN/C195), and that the difference between adjacent level of intraabdominal pressure increased from 12 mmHg (simplex parameter, 0.11 [from 8 to 12 mmHg] and 0.18 [from 12 to 15 mmHg]; Supplemental Digital Content table 5B, http://links.lww.com/ALN/C195). Accordingly, intraabdominal pressure had a significant negative monotonic effect on lung compliance with higher intraabdominal pressures associated with lower lung compliance (Supplemental Digital Content table 7, http://links.lww.com/ALN/C197).

Discussion

In this single-center study comparing intraoperative ventilation with targeted PEEP *versus* standard PEEP at three predefined and clinically relevant intraabdominal pressure levels in patients planned for laparoscopic cholecystectomy, it was found that: (1) pneumoperitoneum increases transpulmonary and respiratory system driving pressure in a nonlinear fashion at an increasing rate when intraabdominal pressure is greater than or equal to 12 mmHg; (3) transpulmonary

Table 2. Ventilation Pressures and Respiratory Mechanics with "Standard PEEP" and "Targeted PEEP" at Three Predefined Intraabdominal Pressure Levels

	Intraabdominal Pressure					
cmH_2O	**mmHg**	**cm H_2O**	**Standard PEEP**	**Targeted PEEP**	**Difference [95% CI]**	***P* Value**
Transpulmonary driving pressure	8	10.8	9 [7–11]	7 [5–8]	2 [0.5–4]	0.010
	12	16.3	10 [7–12]	7 [4–9]	3 [1–5]	0.002
	15	20.4	12 [8–15]	7 [6–9]	4 [2–6]	< 0.001
Respiratory system driving pressure	8	10.8	12 [10–15]	10 [8–11]	3 [1–4]	0.004
	12	16.3	13 [12–15]	11 [9–13]	3 [1–4]	0.001
	15	20.4	17 [14–18]	12 [10–14]	4 [2–6]	< 0.001
Plateau pressure	8	10.8	17 [15–20]	20 [18–21]	2 [1–4]	0.005
	12	16.3	18 [17–20]	25 [23–27]	6 [5–8]	< 0.001
	15	20.4	22 [19–23]	29 [27–31]	8 [6–10]	
						< 0.001
PEEP	8	10.8	5	10		
	12	16.3	5	14		
	15	20.4	5	17		
End-inspiratory pulmonary pressure	8	10.8	3 [0–7]	5 [1–8]	2 [0–4]	0.189
	12	16.3	4 [–1 to 6]	7 [4–9]	4 [1–7]	0.003
	15	20.4	2 [–2 to 6]	9 [3–13]	6 [3–9]	< 0.001
End-expiratory pulmonary pressure	8	10.8	–7 [–10 to –5]	–2 [–5 to 0]	4 [2–6]	0.001
	12	16.3	–8 [–11 to –4]	0 [–3 to 1]	7 [5–10]	< 0.001
	15	20.4	–9 [–14 to –4]	1 [–2 to 5]	10 [6–14]	
						< 0.001
End-inspiratory esophageal pressure	8	10.8	15 [14–18]	15 [13–18]	0 [–2 to 2]	0.867
	12	16.3	17 [14–20]	19 [16–22]	2 [0–4]	0.171
	15	20.4	19 [15–23]	22 [17–25]	1 [–5 to 2]	0.325
End-expiratory esophageal pressure	8	10.8	12 [10–14]	12 [15–15]	0 [–3 to 1]	0.605
	12	16.3	13 [9–16]	14 [13–17]	1 [–4 to 1]	0.293
	15	20.4	14 [9–19]	16 [12–19]	1 [–5 to 2]	0.374

Data are reported as median [25th to 75th percentile]. Airway, transpulmonary, and esophageal pressures are reported in cm H_2O. Abdominal pressure is reported in mmHg and cm H_2O. *P* values reported for univariate analysis. Wilcoxon rank sum test was applied. IAP, intraabdominal pressure; PEEP, positive end-expiratory pressure.

and respiratory system driving pressure have an almost linear relationship and a moderate correlation that decreases as intraabdominal pressure increases; and (3) targeted PEEP decreases transpulmonary driving pressure.

This study has several strengths. First, an esophageal balloon was used to capture pressures that allowed accurate calculations of transpulmonary driving pressure. During intraoperative ventilation under pneumoperitoneum, transpulmonary driving pressure is more informative than respiratory system driving pressure. Second, all titration steps of the study protocol were feasible and in all patients the protocol was followed step-by-step and completed. Third, the study had little exclusion criteria, increasing its generalizability, and had a clear and predefined analysis plan as a measure against reporting bias. Fourth, meticulous multivariable and mixed effect statistical methods were used to control potentially confounding variables, and to include interindividual variability in the various estimates, as well as an analysis of intraabdominal pressure as a quantitative variable and not solely as a dichotomic feature.

Although previous trials reported a small reduction in transpulmonary driving pressure by applying PEEP in an animal model of abdominal hypertension without neuromuscular block,[20] to the best of our knowledge, there is no previous human study that investigates the effects of PEEP titrations linked to *variable* intraabdominal pressure levels in the laparoscopic surgical setting. The results of the current study are in line with findings in recent investigations on titration of PEEP according to certain ventilator parameters, like respiratory system compliance[7] and chest wall and lung compliance.[21] The results of the current study add to our understanding of the effects of PEEP by showing that targeted PEEP reduces transpulmonary and respiratory system driving pressure at all three intraabdominal pressure levels. In addition, the current study found that the intraabdominal pressure level *per se* influences transpulmonary and respiratory system driving pressure and that the effects of targeted PEEP increase at higher intraabdominal pressure levels, building upon findings from previous studies that used conventional intraabdominal pressure levels,[8] as well as a preclinical study that used an animal model of abdominal hypertension.[20] These findings, possibly due to increased alveolar collapse at higher intraabdominal pressure level, suggest a nonlinear thoracoabdominal relationship, especially at

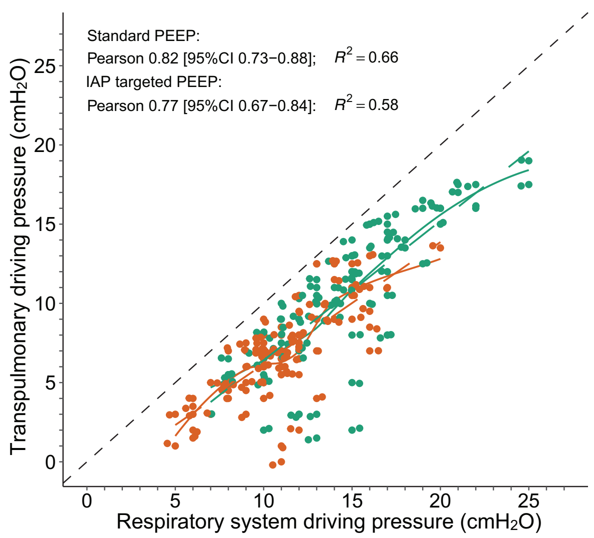

Fig. 2. Scatterplots for transpulmonary driving pressure and respiratory system driving pressure and. *Solid lines* are local polynomial regressions; *dashed lines* are linear regressions. *Green lines* represent the "standard PEEP" group, *orange lines* the "targeted PEEP" group. Overall linear R^2 and Pearson correlation coefficients by group are reported. Transpulmonary and respiratory system driving pressures are reported in cm H_2O. PEEP, positive end-expiratory pressure.

the standard PEEP level, as also shown in the *post hoc* mixed regression analysis. The Bayesian model simplex parameters, which estimate the amount of change at each step of pressure, increase for intraabdominal pressure greater than 12 mmHg; therefore, it can be speculated that thoracoabdominal transmission varies with different intraabdominal pressure levels. The anti-Trendelenburg position may have played a role in mitigating the rate of transmission of intraabdominal pressure to the lungs. Therefore, the potential effects of other surgical positions remain to be tested in future studies.

Interestingly, we observed stable median transpulmonary driving pressure values while rising intraabdominal pressure at targeted PEEP and while median respiratory system driving pressure continued increasing. One possible explanation for this finding is that the applied PEEP counterbalances the rising intraabdominal pressure, avoiding or minimizing alveolar collapse. The resulting increasing difference between the two pressures suggests that at higher intraabdominal pressure, respiratory system driving pressure could not be a good reflection of transpulmonary driving pressure. We observed a similar effect of PEEP on end-expiratory pulmonary pressure across all intraabdominal pressure levels, which suggests an improved alveolar recruitment. An increase in alveolar recruitment not only improves oxygenation,[5] but also leads to more homogeneous ventilation.[6,23] The clinical implications of these improvements, however, remain uncertain. For instance, in critically ill patients with acute respiratory distress syndrome, these improvements did not translate to better clinical outcomes.[24,25]

Postoperative pulmonary complications are a significant source of perioperative morbidity and mortality,[8] and while the protective role of low V_T during intraoperative ventilation is well accepted,[15,26] the role of high PEEP remains highly uncertain.[8,16] Intraoperative respiratory system driving pressure has been suggested to be a risk factor for the development of pulmonary complications after surgery.[3] Whether an intraoperative ventilation strategy directly or indirectly targeting a low respiratory system driving pressure successfully prevents such complications is still debatable. A recently published large trial of general surgery patients found that an open lung approach resulted in a lower incidence of postoperative pulmonary complications. Postoperative pulmonary complications, however, were a secondary outcome of that study.[4] Therefore, current evidence does not allow a definitive conclusion to be drawn.

In the laparoscopic surgery setting, transpulmonary driving pressure could provide better information than respiratory system driving pressure on dynamic lung strain, at least in theory.[24,25] In this regard, data from previous investigations consistently showed how respiratory system compliance decreases with peritoneal insufflation—but the part of the respiratory system (chest wall or lung) that contributes the most is still debated. While chest wall stiffening

Table 3. Correlation between Transpulmonary Driving Pressure and Respiratory System Driving Pressure by PEEP and Intraabdominal Pressure Regime

	Standard PEEP	Targeted PEEP	Intraabdominal Pressure	
	Transpulmonary Driving Pressure		mmHg	cm H_2O
Respiratory system driving pressure	0.89 [0.78–0.95]*	0.90 [0.81–0.95]*	8	10.8
	0.77 [0.60–0.89]*	0.76 [0.55–0.88]*	12	16.3
	0.78 [0.58–0.89]*	0.64 [0.36–0.81]*	15	20.4

Data are reported as Pearson correlation coefficient [95% CI]. PEEP, positive end-expiratory pressure.
*$P < 0.001$.

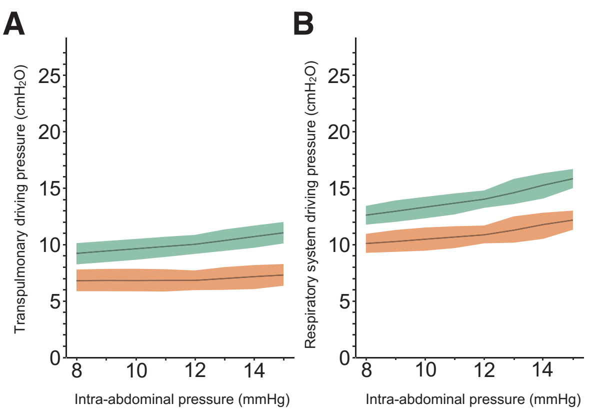

Fig. 3. The marginal effect of intraabdominal pressure from Bayesian multivariable mixed model for (*A*) transpulmonary driving pressure and (*B*) respiratory system driving pressure. *Green lines* represent the "standard PEEP" group, *orange lines* the "targeted PEEP" group. Transparent ribbons are 95% credibility intervals. Transpulmonary and respiratory system driving pressures are reported in cm H_2O and intraabdominal pressure in mmHg. PEEP, positive end-expiratory pressure.

is undisputed,[27–32] there is some difference as far as lung compliance is concerned, with some studies showing a reduction in lung compliance,[27–29] and other showing no pneumoperitoneum related effect.[30–32] Preclinical and clinical studies have shown reductions in transpulmonary driving pressure by applying PEEP.[7,20,21] It must be mentioned, though, that these studies differed from our clinical scenario in many ways. For instance, preclinical evidence was obtained at different intraabdominal pressure levels of PEEP without using neuromuscular blocking agents.[20] Additionally, to the best of our knowledge, no human study has been performed that investigated the effects of PEEP titrations linked to variable intraabdominal pressure levels during surgery. Important to notice is that the results of the current clinical study are in line with findings in recently published studies on PEEP titration to respiratory system compliance during laparoscopic surgery,[7] and on PEEP plus recruitment maneuver at a fixed intraabdominal pressure level.[21]

The current study suggests a moderate-to-strong correlation between transpulmonary and respiratory system driving pressure across all three intraabdominal pressure levels, independent from the two levels of PEEP tested. It cannot be excluded that this was caused by the use of repeated recruitment maneuvers before each PEEP titration. While targeted PEEP at high intraabdominal pressure resulted in comparable driving pressure as standard PEEP at low intraabdominal pressure, the intraabdominal pressure level can have an effect on respiratory pressures and mechanics, *per se*. These findings, at least in part, suggest that performing surgery at a lower intraabdominal pressure results in a low transpulmonary driving pressure, *per se*. Surgery at a lower intraabdominal pressure, instead of surgery with high PEEP, could have several advantages. For instance, high PEEP may increase lung static strain, potentially leading to more inflammation.[33] High PEEP may also negatively affect right ventricular function.[34,35] In addition, high PEEP could favor the development of pleural effusions through compression of lymphatic vessels as shown in previous trials.[4,19,36] Future studies of strategies that may affect transpulmonary driving pressure, and their effects on clinical outcomes, should therefore not only focus on the best level of PEEP, but probably also on the best intraabdominal pressure. As shown before, the best intraabdominal pressure is not necessarily a high intraabdominal pressure.[22]

This study has several limitations. As previously mentioned, PEEP was not repeatedly titrated, and all titrations occurred before the start of the surgical procedure itself in this study. To prevent a possible carryover effect between the successive intraabdominal pressure steps, each new step in the study protocol started with a reduction of PEEP to 5 cm H_2O, plus a recruitment maneuver. Nevertheless, a carryover effect from the preceding PEEP titrations cannot be ruled out entirely. It must be acknowledged that the effect of high PEEP on transpulmonary pressure and lung compliance was studied in a particular surgical positioning, and it could be that effects are different when another surgical position is used. In addition, this study compared only two PEEP levels, *i.e.*, without individualization. We did not record cardiac output, nor did we monitor for hemodynamic instability during the protocol period. Moreover, the study protocol did not allow us to determine end-expiratory volumes or the extent of atelectasis or overdistension.[37–39] Additionally, we measured plateau pressure by using an end-inspiratory occlusion of 0.5 s. Thus, it is possible that we did not reach a static plateau pressure at end-inspiration, likely yielding a minimal overestimation of the driving pressure. However, this method and short duration of occlusion has been previously used in patients undergoing general anesthesia to estimate plateau pressure.[40] Further, most ventilators actually used in anesthesia do not allow longer periods of inspiratory occlusion. Also, due to the specific esophagus probe filling procedure, comparison with other probes of different inflating volumes have to be interpreted with some caution. Moreover, since our main objective was the transpulmonary driving pressure, we did not perform a calibration of absolute values, thus, interpretation on individual values such as end-expiratory pulmonary pressure must be done with caution. Finally, we conceived our study as a physiologic proof of concept with a power estimation for a limited number of patients and without prespecified correction for multiple comparisons. Therefore, our result should be seen as exploratory. Esophageal monitoring can be cumbersome in operating room conditions and may represent only an estimation of regional pressure. Due to this technique, related pitfalls relying on respiratory system driving pressure is appealing, provided that its value can be reliably related to the real lung strain.

In conclusion, in this cohort of patients planned for laparoscopic cholecystectomy, using three different but relevant intraabdominal pressure levels, transpulmonary driving pressure increased at higher intraabdominal pressure levels. These effects could be counterbalanced with targeted PEEP, with the strongest effect at the highest intraabdominal pressure level. However, lowering intraabdominal pressure could be a more attractive approach to lower the transpulmonary driving pressure than using targeted PEEP.

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Competing Interests

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