

Individual Positive End-expiratory Pressure Settings Optimize Intraoperative Mechanical Ventilation and Reduce Postoperative Atelectasis

Sérgio M. Pereira, M.D., Mauro R. Tucci, M.D., Ph.D., Caio C. A. Morais, P.T., M.Sc.,
 Cláudia M. Simões, M.D., Ph.D., Bruno F. F. Tonelotto, M.D., Michel S. Pompeo, M.D.,
 Fernando U. Kay, M.D., Ph.D., Paolo Pelosi, M.D., F.E.R.S., Joaquim E. Vieira, M.D., Ph.D.,
 Marcelo B. P. Amato, M.D., Ph.D.



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ABSTRACT

Background: Intraoperative lung-protective ventilation has been recommended to reduce postoperative pulmonary complications after abdominal surgery. Although the protective role of a more physiologic tidal volume has been established, the added protection afforded by positive end-expiratory pressure (PEEP) remains uncertain. The authors hypothesized that a low fixed PEEP might not fit all patients and that an individually titrated PEEP during anesthesia might improve lung function during and after surgery.

Methods: Forty patients were studied in the operating room (20 laparoscopic and 20 open-abdominal). They underwent elective abdominal surgery and were randomized to institutional PEEP (4 cm H₂O) or electrical impedance tomography–guided PEEP (applied after recruitment maneuvers and targeted at minimizing lung collapse and hyperdistension, simultaneously). Patients were extubated without changing selected PEEP or fractional inspired oxygen tension while under anesthesia and submitted to chest computed tomography after extubation. Our primary goal was to individually identify the electrical impedance tomography–guided PEEP value producing the best compromise of lung collapse and hyperdistension.

Results: Electrical impedance tomography–guided PEEP varied markedly across individuals (median, 12 cm H₂O; range, 6 to 16 cm H₂O; 95% CI, 10–14). Compared with PEEP of 4 cm H₂O, patients randomized to the electrical impedance tomography–guided strategy had less postoperative atelectasis (6.2 ± 4.1 vs. 10.8 ± 7.1% of lung tissue mass; *P* = 0.017) and lower intraoperative driving pressures (mean values during surgery of 8.0 ± 1.7 vs. 11.6 ± 3.8 cm H₂O; *P* < 0.001). The electrical impedance tomography–guided PEEP arm had higher intraoperative oxygenation (435 ± 62 vs. 266 ± 76 mmHg for laparoscopic group; *P* < 0.001), while presenting equivalent hemodynamics (mean arterial pressure during surgery of 80 ± 14 vs. 78 ± 15 mmHg; *P* = 0.821).

Conclusions: PEEP requirements vary widely among patients receiving protective tidal volumes during anesthesia for abdominal surgery. Individualized PEEP settings could reduce postoperative atelectasis (measured by computed tomography) while improving intraoperative oxygenation and driving pressures, causing minimum side effects. (ANESTHESIOLOGY 2018; 129:1070-81)

LUNG protective ventilation has been shown to improve outcomes in patients undergoing general anesthesia.¹⁻⁴ Anesthesia, paralysis, and mechanical ventilation under high concentrations of oxygen without adding positive end-expiratory pressure (PEEP) all result in persistent atelectasis, lung heterogeneities, and postoperative pulmonary complications.^{2,5-7} High driving pressures (ΔP) during anesthesia have been associated with the development of postoperative pulmonary complications, including adult respiratory distress syndrome.^{8,9} The presence of a high ΔP indicates cyclic lung overstress caused by atelectasis and lung heterogeneities, often exacerbated by suboptimal ventilator settings.^{10,11} Thus, a lower intraoperative ΔP has been associated with a reduction in postoperative pulmonary complications.^{8,9}

Editor's Perspective

What We Already Know about This Topic

- In patients with adult respiratory distress syndrome, physiologic tidal volume and positive end-expiratory pressure (PEEP) are protective
- In patients without lung diseases undergoing mechanical ventilation under general anesthesia, optimal PEEP is unknown

What This Article Tells Us That Is New

- Optimal positive end-expiratory pressure (PEEP) values for patients with normal lungs and under general anesthesia vary significantly
- Application of individualized optimal PEEP intraoperatively not only reduces driving pressure and improves respiratory compliance and oxygenation but also reduce the incidence and severity of postoperative atelectasis

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 1057. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a video abstract. This article has an audio podcast. This article has a visual abstract available in the online version. Partial results were presented as a poster at ESICM Lives in Milan, Italy, October 1-5, 2016. S.M.P. and M.R.T. contributed equally to this article.

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Recent analyses of protective strategies have suggested the use of more physiologic tidal volumes (V_T ; $V_T = 6$ to 8 ml/kg of ideal body weight) in combination with fixed, minimum PEEP levels, although with recommendations that vary from 2 up to 6 cm H_2O .¹⁻⁴ Although the protective role of more physiologic tidal volume (V_T) has been strongly suggested, no agreement exists on the value of optimal PEEP. A recent trial showed no benefit of high PEEP of 12 cm H_2O versus ≤ 2 cm H_2O , but harms including hemodynamic instability and increased requirement of fluid administration.¹² Therefore, low PEEP (≤ 2 cm H_2O) was recommended.^{4,13} Meanwhile, others have suggested the use of moderate levels of PEEP (5 to 8 cm H_2O),^{2,9,14} advocating its preventive role against postoperative atelectasis. Such lack of consensus occurs, in part, because PEEP is not typically individualized according to patient physiology. Evidence suggests that one fixed value of PEEP is unlikely to fit all patients, with large variability in PEEP requirements caused by individual characteristics, such as chest wall dimensions and shape, abdominal content, lung weights, and pleural pressures.¹⁵⁻²¹

This study evaluated the impact of the optimized PEEP guided by electrical impedance tomography (PEEP-EIT) versus fixed PEEP of 4 cm H_2O applied during the intraoperative period, in patients with healthy lungs and submitted to abdominal surgery. We hypothesized that PEEP-EIT would vary among different patients and that it would reduce postoperative atelectasis. Our primary goal was to individually identify the PEEP-EIT value that produced the best possible compromise of lung collapse and hyperdistention. Our secondary aim was to observe the effects of such PEEP-EIT on the postoperative atelectasis measured by computed tomography scan after extubation. Additional exploratory end points were the impact of PEEP selection (according to randomization) on pulmonary function and hemodynamics.

Materials and Methods

Between August 2014 and April 2016, 40 eligible patients undergoing elective abdominal surgery were included in the study after obtaining Institutional Review Board approval and written informed consent. This trial was registered at clinicaltrials.gov (trial registration: NCT02314845). All patients were submitted to anesthesia induction, ventilation with PEEP of 4 cm H_2O , first recruitment maneuver followed by PEEP titration, and second recruitment maneuver. Then, patients were randomized to one of two treatment arms: PEEP titrated by EIT (PEEP-EIT), within the range

from 4 to 20 cm H_2O or a fixed PEEP of 4 cm H_2O (PEEP4) (fig. 1A). The randomization was stratified by type of surgery. The inclusion criteria were abdominal surgery and age above 18 years old. Exclusion criteria were American Society of Anesthesiologists Physical Status III or greater and moderate/severe obstructive or restrictive pulmonary disease.

Intravenous anesthesia was induced with patients lying supine. After insertion of intravenous and arterial lines, an EIT belt was placed at the fifth intercostal space, and the EIT monitoring (Enlight 1800, Timpel, Brazil) was started with continuous recording. All patients were preoxygenated with 100% oxygen before intubation.

Mechanical ventilation was started under volume-controlled ventilation with fractional inspired oxygen tension (F_{IO_2}) = 0.5, PEEP = 4 cm H_2O , $V_T = 6$ to 7 ml/kg of predicted body weight,²² an inspiratory pause of 30%, and respiratory rate was adjusted to maintain

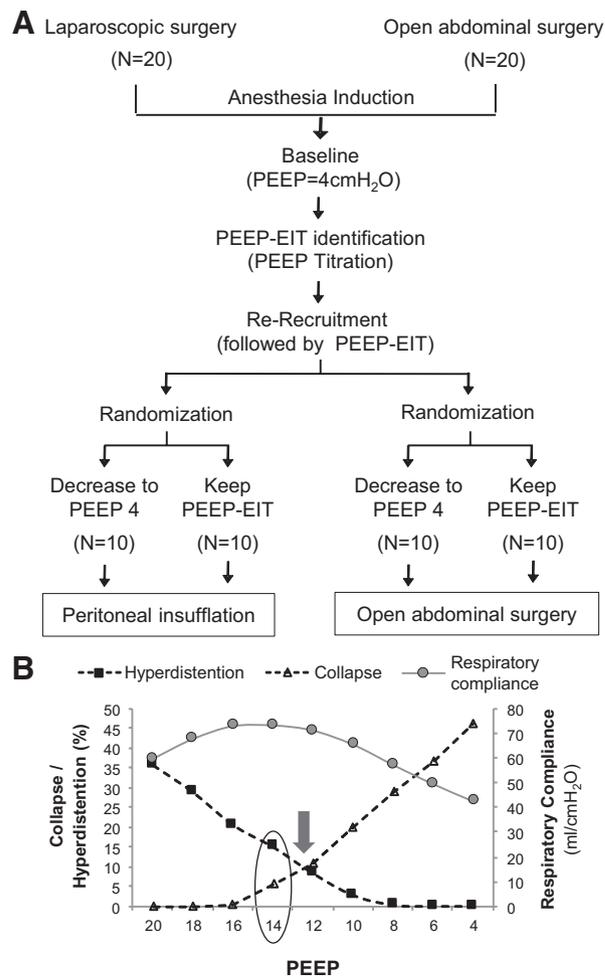


Fig. 1. A, Flowchart of the study. B, Criteria to choose positive end-expiratory pressure (PEEP) titrated by electrical impedance tomography (PEEP-EIT). PEEP-EIT was considered as the nearest PEEP above the crossing of the curves representing overdistention and collapse, indicating a mechanical compromise at which both lung collapse and hyperdistention were minimized.

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end-tidal carbon dioxide between 35 and 45 mmHg. The synchronized pressure-flow sensor of the EIT monitor was connected to the proximal airway. After recording the baseline EIT signals, all patients (in both arms) were submitted to a recruitment maneuver in pressure-controlled ventilation mode with 20 cm H₂O of PEEP and inspiratory pressures reaching 40 cm H₂O for 2 min. At this PEEP level, a decremental PEEP-titration maneuver was started in volume-controlled ventilation mode, decreasing PEEP in steps of 2 cm H₂O every 40 s, and keeping constant respiratory rate (20 breaths/min), inspiratory pause of 30%, and V_T = 6 ml/kg. At the end of the procedure, the EIT monitor automatically plotted a graph showing the percentage of overdistended and collapsed lung units (corresponding to the percent mass of collapsed or overdistended lung-tissue) at each PEEP. PEEP-EIT was considered as the nearest PEEP above the crossing of the curves representing overdistension and collapse (fig. 1B), indicating a mechanical compromise where both lung collapse and overdistension were minimized.

After the decremental PEEP titration (performed in all patients before randomization), a new recruitment maneuver was performed, and PEEP-EIT was applied for 2 min, only for monitoring purposes. Subsequently, the patient was randomized and, according to group allocation, the PEEP-EIT was then maintained (PEEP-EIT arm) or reduced to 4 cm H₂O (PEEP4 arm). This randomized PEEP level was maintained throughout surgery, until extubation.

Data acquisition in laparoscopic and open abdominal surgery occurred in several time points: baseline (after intubation), during PEEP titration, after randomization, within 1 h of surgery, and before extubation. Data acquisition in patients undergoing laparoscopic surgery also occurred at the start of pneumoperitoneum and before pneumoperitoneum deflation. Mechanical ventilation, EIT, and hemodynamic data were collected. Arterial blood gas samples were also analyzed during surgery (fig. 2, A and B). Mechanical

ventilation parameters, such as RR and FIO₂, could be changed according to arterial blood gas results or SpO₂. Fluid administration, pain management, vasoactive drugs, and blood transfusion were implemented according to routine protocols.

Weaning was performed under pressure-support mode, keeping FIO₂ at 50% and maintaining PEEP according to the patient's randomization (*i.e.*, at 4 cm H₂O in controls, and at PEEP-EIT for the treatment arm). Thirty to 60 min after extubation, a chest computed tomography scan was obtained, during which patients were instructed to perform an expiratory hold at functional residual capacity. Ten slices were optimally selected to interpolate and calculate the percentage of nonaerated lung mass tissue (densities between -200 and +100 UH).²³

The primary outcome of this trial was to identify the PEEP value, for each patient, that produced the best possible compromise of lung collapse and hyperdistention during a PEEP titration procedure using EIT. The secondary end point was to calculate the amount of atelectasis, as the percentage of lung mass, evaluated by chest computed tomography scan after extubation. Additional exploratory end points were the impact of PEEP selection (according to randomization) on pulmonary function and hemodynamics. Additional information on some procedures is provided in the Supplemental Digital Content, <http://links.lww.com/ALN/B784>.

Statistical Analysis

The sample size was estimated for our secondary end point, the amount of atelectasis. A previous study²⁴ observed, in patients ventilated with and without PEEP (=6 cm H₂O), a median area of atelectasis postoperatively of 5.2 cm² (range 1.6 to 12.2) versus 8.5 cm² (3–23.1). A sample size of 40 patients (20 patients in each PEEP arm) would be needed to observe this difference, assuming $\alpha = 0.05$ and power of 85%, using two-tailed Wilcoxon-Mann-Whitney

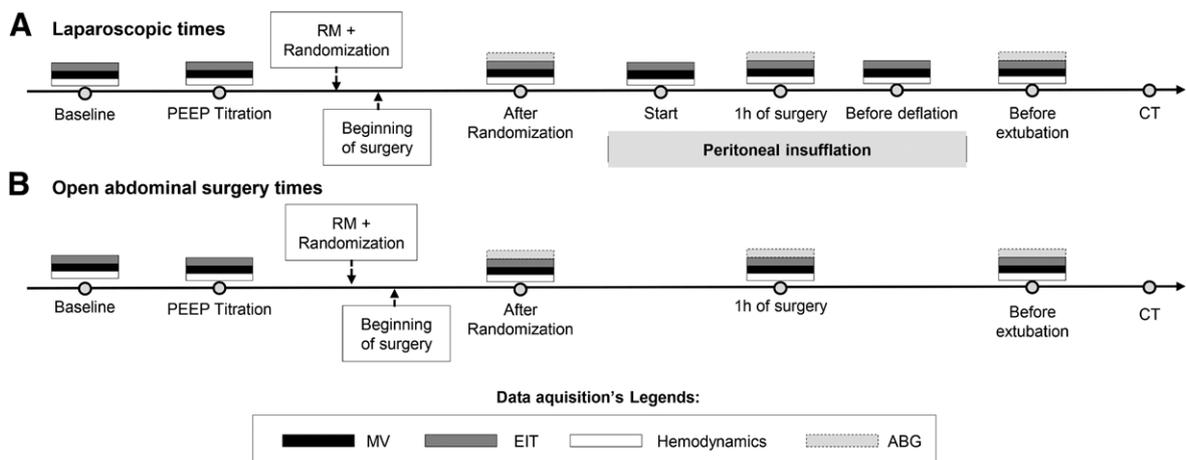


Fig. 2. Data collection times in laparoscopic (A) and open abdominal surgery (B). ABG, arterial blood gas; CT, computed tomography; EIT, electrical impedance tomography; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; RM, recruitment maneuver.

test (asymptotic relative efficiency method) with software G*Power 3.1²⁵ and considering a data loss of 10%.

Normal distribution for continuous variables was determined using the Shapiro-Wilk test and, accordingly, the results were reported as mean \pm SD and median (interquartile range). Unpaired *t* tests or Mann-Whitney tests were used for univariate analyses of continuous variables. For correlation between two variables, the Pearson correlation test was used.

For the analysis of variables collected at many time points during surgery and for computed tomography collapse, a mixed-model analysis, without random factors, was performed using the following variables as fixed factors: type of surgery (laparoscopic and open), time (from “PEEP-EIT,” during PEEP titration, to “before extubation”), group (PEEP-EIT arm or PEEP4 arm), and the interaction between time and group. For comparisons between time points the Sidak correction test was used. Mean values for driving pressure, mean arterial pressure, PaO₂/FIO₂, and respiratory compliance after randomization were calculated for one or both types of surgery (laparoscopic and open), representing the average of three time points during surgery.

No data nor outlier values were excluded. The amount of missing data is less than 5%, in general, with no single variable presenting more than 15% of missing data. No data imputation was performed. SPSS 17 for Windows (SPSS Inc., USA) and GraphPad Prism V 6 (GraphPad Software, USA) were used for the statistical analyses and to plot the graphs. Statistically significant values were considered to have *P* values less than 0.05 using two-tailed tests.

Results

A total of 40 patients were included in this study. Patients' characteristics and comorbidities are summarized in table 1 and table E1 in the Supplemental Digital Content (<http://links.lww.com/ALN/B784>). No complication associated with the study was observed in any participant.

After anesthesia induction and intubation, when all patients received PEEP = 4 cm H₂O (before recruiting maneuvers), there were no statistically significant differences in respiratory variables between the two study arms (table 2). Equivalent respiratory variables were also observed after recruitment maneuver, when patients in both study arms were briefly submitted, during PEEP titration, to PEEP-EIT (table 2).

Primary Outcome: Identified PEEP

Before randomization, PEEP-EIT was assessed by for all patients after a recruiting maneuver. The median PEEP-EIT was 12 cm H₂O (10 to 14; 95% CI, 10–14; table 3 and fig. E1 in the Supplemental Digital Content (<http://links.lww.com/ALN/B784>)). Patients submitted to laparoscopic surgery exhibited statistically significantly higher PEEP-EIT than patients submitted to open surgery (13.5 \pm 1.6 *vs.* 10.2 \pm 2.3 cm H₂O; *P* < 0.001). Of note, PEEP

Table 1. Baseline Characteristics of the Patients

Demographic and Clinical Variables	All (n = 40)	PEEP4 (n = 20)	PEEP-EIT (n = 20)
Age, median (IQR), yr	52.5 (26–74)	54.2 (33–68)	50.7 (26–74)
Male sex, n (%)	18 (45.0)	8 (40.0)	10 (50.0)
Weight, mean \pm SD, kg	77.9 \pm 15.6	79 \pm 15.9	76.8 \pm 15.6
Predicted body weight, mean \pm SD, kg	56.4 \pm 9.5	54.3 \pm 9.9	58.6 \pm 8.8
Body mass index, mean \pm SD, kg/m ²	29.5 \pm 4.3	30.6 \pm 4.2	28.3 \pm 4.2
Thoracic perimeter, mean \pm SD, cm	100.4 \pm 8.6	102 \pm 9.0	99 \pm 8.0
Type of Surgery			
Urology, n (%)	13 (32.5)	5 (25)	8 (40)
Gastric, n (%)	19 (47.5)	10 (50)	9 (45)
Gynecology, n (%)	8 (20)	5 (25)	3 (15)
ASA Physical Status I, n (%)	12 (30)	6 (30)	6 (30)
ASA Physical Status II, n (%)	28 (70)	14 (70)	14 (70)
Hypertension, n (%)	18 (45)	8 (40)	10 (50)
Hypothyroidism, n (%)	3 (7.5)	1 (5)	2 (10)
Diabetes, n (%)	7 (17.5)	2 (10)	5 (25)
Chronic kidney disease, n (%)	1 (2.5)	0 (0)	1 (5)
Smoking status			
Never, n (%)	27 (67.5)	16 (80)	11 (55)
Former, n (%)	5 (12.5)	2 (10)	3 (15)
Current, n (%)	8 (10)	2 (10)	6 (30)
Active cancer, n (%)	14 (35)	5 (25)	9 (45)
Chemotherapy, n (%)	0 (0)	0 (0)	0 (0)

Chronic kidney disease as defined according to Kidney Disease: Improving Global Outcomes. ASA, American Society of Anesthesiologists; IQR, interquartile range; PEEP4, PEEP of 4 cm H₂O; PEEP-EIT, PEEP guided by electrical impedance tomography.

requirements for the laparoscopic patients were assessed before abdominal insufflation of CO₂. There was some correlation ($R^2 = 0.371$, *P* < 0.001) between body mass index and PEEP-EIT (fig. 3), which partially explained such difference in PEEP-EIT (patients in the open surgery group had a lower body mass index, requiring a lower PEEP-EIT).

Secondary Outcome: Postoperative Collapse

After extubation and anesthesia recovery, the whole-lung computed tomography evaluation confirmed the reduction in atelectasis, with a significantly lower percentage of collapsed lung tissue in the PEEP-EIT arm (percent of nonaerated tissue = 6.2 \pm 4.1% *vs.* 10.8 \pm 7.1%; PEEP-EIT *vs.* PEEP4, respectively; *P* = 0.017; fig. 4). The amount of atelectasis in the two types of surgery was not different (*P* = 0.457). Representative images of computed tomography (after surgery) and EIT (during surgery) are shown in figure 5.

Exploratory Outcomes: PEEP, Body Mass Index, and Driving Pressure

When comparing ΔP before and after PEEP titration (*i.e.*, comparing ΔP at PEEP = 4 cm H₂O [after anesthesia induction] *vs.* the ΔP at the titrated-PEEP [after a recruiting

Table 2. Ventilation Parameters

Time of Acquisition	Parameters	Laparoscopic (n = 20) Randomized Group			Open Surgery (n = 20) Randomized Group		
		PEEP4 (n = 10)	PEEP-EIT (n = 10)	P Value	PEEP4 (n = 10)	PEEP-EIT (n = 10)	P Value
Baseline	V _T /Kg (ml/kg)	7±0.7	6.4±0.5	0.073	6.6±0.5	6.2±0.7	0.144
	PEEP (cmH ₂ O)	4.2±0.3	4.1±0.4		4.1±0.1	4.4±0.4	
	Plateau pressure (cmH ₂ O)	15.7±2.4	13.9±3.3	0.195	13.3±2.5	13.4±1.9	0.883
	Compliance (ml/cmH ₂ O)	33.5±8.1	37.7±9.7	0.317	42.1±15.7	43.5±7.9	0.807
	Driving pressure (cmH ₂ O)	11.6±2.5	9.8±3.1	0.188	9.3±2.5	9.1±1.7	0.869
	Collapse on EIT (%)	44.6±15.4	41.7±18.0	0.711	35±16.1	31.3±9.2	0.530
During titration (at PEEP-EIT)	V _T /Kg (ml/kg)	7.1±0.5	6.7±0.5	0.086	6.8±0.5	6.5±0.6	0.125
	PEEP (cmH ₂ O)	14.3±1.5	12.9±1.6		10.2±2.3	10.3±2.3	
	Plateau pressure (cmH ₂ O)	19.5±2.0	18.1±1.9	0.130	16.1±3.1	16.8±3.3	0.660
	Compliance (ml/cmH ₂ O)	77.1±14.0	75.3±8.6	0.742	75.9±18.0	71.9±15.7	0.601
	Driving pressure (cmH ₂ O)	5.3±0.7	5.2±0.7	0.796	6.0±1.3	6.5±1.1	0.336
	Collapse on EIT (%)	6.5±5.6	4.5±3.9	0.375	3.6±1.8	5.4±2.8	0.097
After randomization (selected PEEP)	V _T /Kg (ml/kg)	7.1±0.7	6.5±0.8	0.071	6.6±0.4	6.3±0.6	0.206
	PEEP (cmH ₂ O)	3.8±0.3	13.2±1.4	<0.001	3.9±0.3	10.1±2.0	<0.001
	Plateau pressure (cmH ₂ O)	13.7±1.4	18.7±2.0	<0.001	11.7±1.4	16.6±3.1	<0.001
	Compliance (ml/cmH ₂ O)	39.6±7.2	67.6±6.7	<0.001	48.8±13.2	66.2±14.2	0.011
	Driving pressure (cmH ₂ O)	9.8±1.4	5.5±0.8	<0.001	7.7±1.5	6.5±1.3	0.070
	Collapse on EIT (%)	42.5±12.6	10.3±10.2	<0.001	29.8±14.2	8.5±5.1	<0.001

Data are expressed as mean ± SD; V_T/Kg is expressed in ml/kg; PEEP, plateau pressure, and driving pressure are expressed in cmH₂O; Respiratory compliance is expressed in ml/cmH₂O; "Collapse on EIT": collapse on electrical impedance tomography is expressed as percentage of total lung mass; PEEP4, group randomized to PEEP of 4 cm H₂O; PEEP-EIT, group randomized to PEEP titrated by EIT. *P* (*t* test) for the difference between PEEP4 and PEEP-EIT in the same type of surgery (laparoscopic or open surgery). *P* values less than 0.05 are shown in bold.

EIT, electrical impedance tomography; PEEP, positive end-expiratory pressure; PEEP4, PEEP of 4 cm H₂O; PEEP-EIT, PEEP guided by electrical impedance tomography; V_T, tidal volume.

Table 3. Median Values of Titrated PEEP by Electrical Impedance Tomography

Criteria to Choose PEEP	All Patients (n = 40)	Laparoscopic (n = 20) Randomized Group		Open Surgery (n = 20) Randomized Group	
		PEEP4 (n = 10)	PEEP-EIT (n = 10)	PEEP4 (n = 10)	PEEP-EIT (n = 10)
PEEP-EIT, cmH ₂ O	12 (10–14)	14 (12–16)	14 (12–14)	10 (10–12)	10 (8–10)

Data are expressed as median (interquartile range).

EIT, electrical impedance tomography; PEEP, positive end-expiratory pressure; PEEP4, PEEP of 4 cm H₂O; PEEP-EIT, PEEP guided by electrical impedance tomography.

maneuver]), we observed a statistically significant reduction from 9.9±2.6 to 5.7±1.1 cm H₂O (*P* < 0.001). This reduction in Δ*P* was associated with a marked reduction in lung collapse (from an average of 38±15% to 6±4% of lung parenchyma; *P* < 0.001) and correlated with body mass index: the higher the body mass index, the greater the response to recruitment and the larger the reduction in Δ*P* (fig. 6; *R*² = 0.454, *P* < 0.001).

After randomization, PEEP was kept at the PEEP-EIT within the PEEP-EIT arm and decreased to 4 cm H₂O within the PEEP4 arm. Consequently, patients in the PEEP-EIT arm showed higher PEEP and higher plateau pressure (V_T was kept constant, table 2 and table E2 in the Supplemental Digital Content, <http://links.lww.com/ALN/B784>). During surgery, we observed a marked increase in Δ*P* in the PEEP4 arm when compared with PEEP-EIT: mean values for both types of surgeries of 11.6±3.8 versus 8.0±1.7 cm H₂O (*P* < 0.001 for the PEEP arm factor

of the mixed model analysis; fig. 7). Respiratory-system compliance decreased for the PEEP4 arm: mean values of 35.4±13.4 versus 54.3±13.9 ml/cmH₂O (*P* < 0.001 for the PEEP arm factor; fig. E2). Parallel to these changes, ventilation in dependent lung zones decreased (fig. E3 in the Supplemental Digital Content, <http://links.lww.com/ALN/B784>), and oxygenation worsened, especially in the laparoscopy group (fig. 8). These deteriorating changes were especially observed in the PEEP4 arm undergoing laparoscopic surgery and were associated with progressive, dependent lung collapse that persisted until the end of surgery, as shown by the EIT-derived estimates of lung collapse (table E2 in the Supplemental Digital Content, <http://links.lww.com/ALN/B784>). As for open abdominal surgery, within 1 h of surgery and before extubation, neither Δ*P* nor collapse on EIT was statistically different between groups (table E2 in the Supplemental Digital Content, <http://links.lww.com/ALN/B784>).

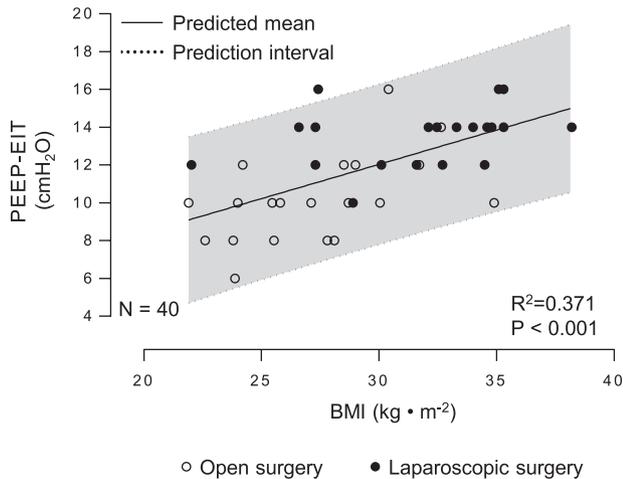


Fig. 3. Correlation and prediction interval of positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT) of all patients and body mass index (BMI). Open circles represent open surgery and closed circles represent laparoscopic surgery.

Respiratory parameters were better preserved, with differences between arms exacerbated in the laparoscopic procedures. Minutes after peritoneal insufflation, the difference in ΔP between study arms reached 6.4 cm H₂O (95% CI, 3.4–9.4; $P = 0.001$), with the PEEP-EIT arm always presenting lower ΔP .

Along the intraoperative period, the differences in PaO₂/FiO₂ ratio mirrored the physiologic alterations described above. Patients in the PEEP-EIT arm presented higher PaO₂/FiO₂ ratios, with pronounced and statistically significant differences when considering the laparoscopic procedure (mean

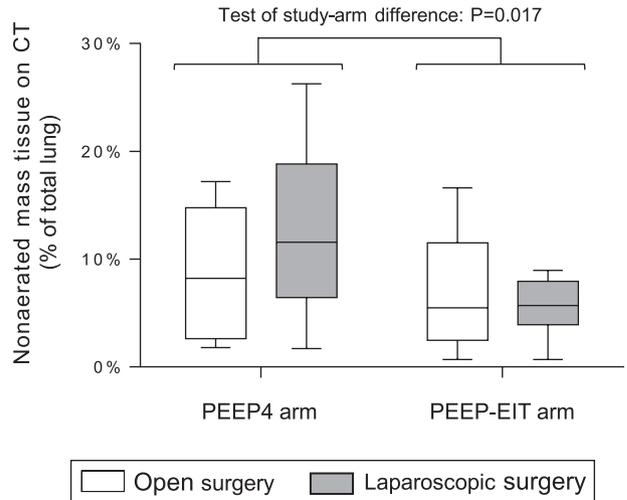


Fig. 4. Box plot (median with 25th and 75th percentiles) of nonaerated mass tissue on computed tomography after extubation. Gray boxes represent patients submitted to laparoscopic surgery, and white boxes represent patients submitted to open surgery. The positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT) arm had less atelectasis than PEEP4 arm after extubation. CT, computed tomography; PEEP4, PEEP of 4 cm H₂O.

of all samples along the surgery, PEEP-EIT *vs.* PEEP4 arm, 435 ± 62 *vs.* 266 ± 76 mmHg, $P < 0.001$; fig. 8). There is no difference in PaO₂/FiO₂ ratio between the two types of surgery ($P = 0.064$). FiO₂ was set at 0.5 throughout the surgery in all but one patient of the PEEP4 arm (submitted to open surgery), in which FiO₂ was increased to 0.6. The PaCO₂ was not significantly different between the study arms ($P = 0.805$ in laparoscopic surgery *vs.* $P = 0.964$ in open surgery), but it

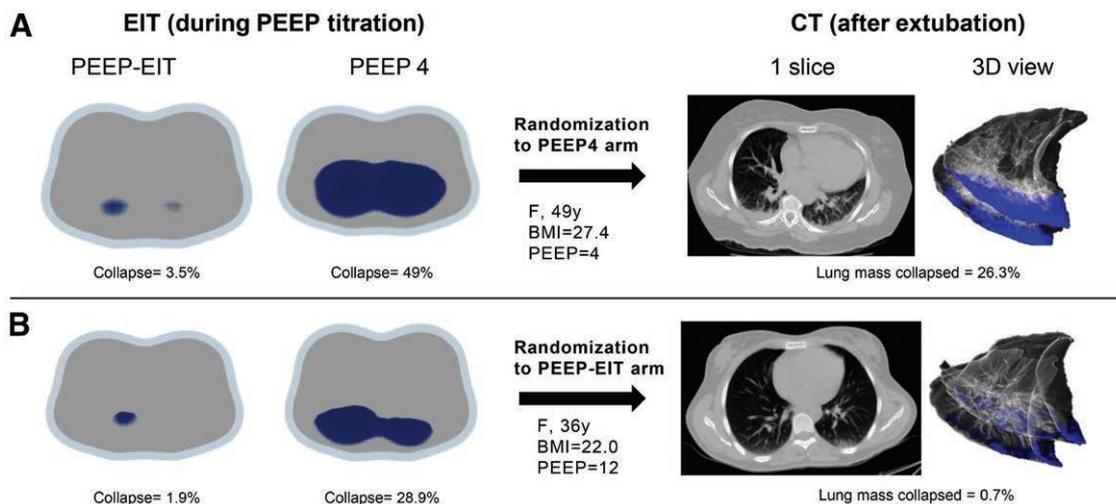


Fig. 5. Examples of electrical impedance tomography (EIT) images (at positive end-expiratory pressure guided by electrical impedance tomography [PEEP-EIT] and PEEP of 4 cm H₂O) and computed tomography images (after extubation) of two patients: in (A) a patient randomized for PEEP4 arm, and in (B) a patient randomized for PEEP-EIT arm. At left, EIT images show in blue the estimative of lung mass collapsed during PEEP titration in two values of PEEP (PEEP-EIT and PEEP of 4 cm H₂O). At right, one axial slice of the lung computed tomography and three-dimensional reconstruction of the lungs show the collapsed lung in blue (areas between -200 to +100 UH). BMI, body mass index; CT, computed tomography.

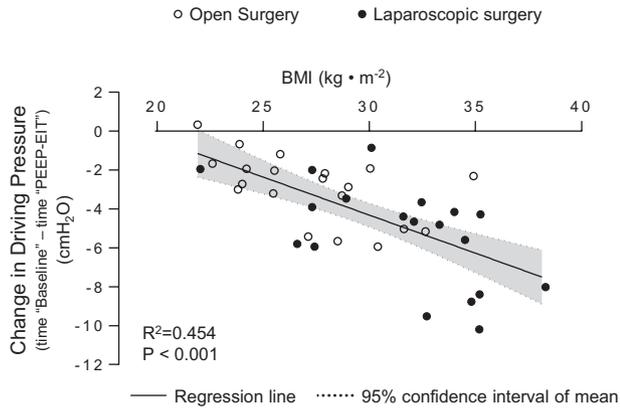


Fig. 6. Correlation of body mass index (BMI) and drop in driving pressure between time “baseline” (using positive end-expiratory pressure [PEEP] of 4 cm H₂O) and “during titration” (at PEEP titrated by electrical impedance tomography [PEEP-EIT]). Open circles represent open surgery, and closed circles represent laparoscopic surgery.

was consistently higher in the laparoscopic than in the open surgery procedure ($P = 0.014$; fig. E4 in Supplemental Digital Content, <http://links.lww.com/ALN/B784>).

Exploratory Outcomes: Anesthetic Management, Hemodynamics, and Length of Hospital Stay

The anesthetic management of patients is shown in table 4. In both types of surgery, a high percentage of patients needed vasoactive drugs during the recruitment maneuvers, but none needed continuous infusion throughout surgery. There were no differences between PEEP4 and PEEP-EIT arms in urine output or total fluids per hour in both types of surgery.

Patients submitted to open surgery were commonly submitted to neuroaxial anesthesia without any difference between the two study arms. No difference was observed in mean arterial pressure (mean of three time points during both types of surgery: PEEP-EIT of 80 ± 14 vs. PEEP4 of 78 ± 15 mmHg; $P = 0.821$) over time (fig. 9). Length of hospital stay was also not different between the two study arms (fig. E5 in Supplemental Digital Content, <http://links.lww.com/ALN/B784>). The length of both anesthesia and surgery, however, were longer in the PEEP4 arm when compared with the PEEP-EIT arm ($P = 0.013$ and $P = 0.009$, respectively).

Discussion

This pilot, randomized study tested the physiologic impact of individualized PEEP-EIT in anesthetized patients with healthy lungs receiving protective ventilation (V_T strictly lowered to 6 ml/kg, predicted body weight). The main findings were: (1) PEEP-EIT had a wide distribution among patients; (2) the beneficial effects persisted after extubation: those patients ventilated with PEEP-EIT presented less atelectasis on the chest computed tomography; (3) PEEP-EIT minimized lung collapse, reduced ΔP , and improved oxygenation and respiratory system compliance when compared with standard PEEP of 4 cm H₂O; (4) patients receiving PEEP-EIT did not present intraoperative hemodynamic instability nor did they require more vasoactive drugs or fluids.

Identified PEEP

The EIT has an algorithm that estimates recruitable alveolar collapse and hyperdistension during a decremental PEEP

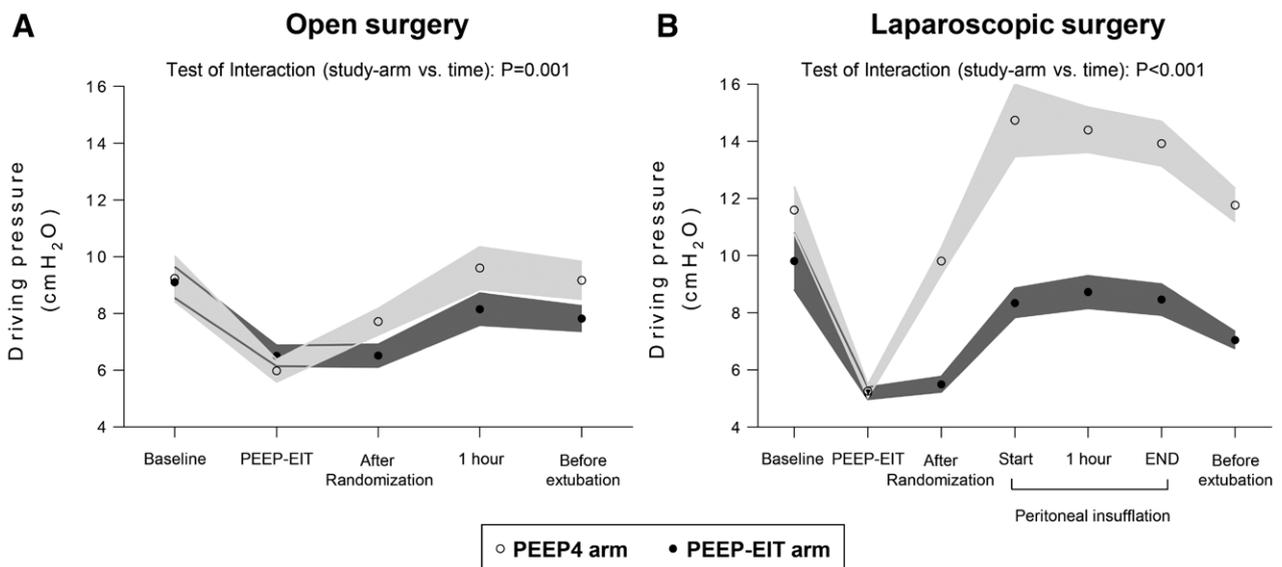


Fig. 7. Mean driving pressure during intraoperative period in open surgery (A) and laparoscopic surgery (B). Shaded areas represent standard error of mean. Closed circles represent positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT) arm, and open circles represent PEEP of 4 cm H₂O (PEEP4) arm. In both types of surgery, driving pressure was lower in PEEP-EIT arm.

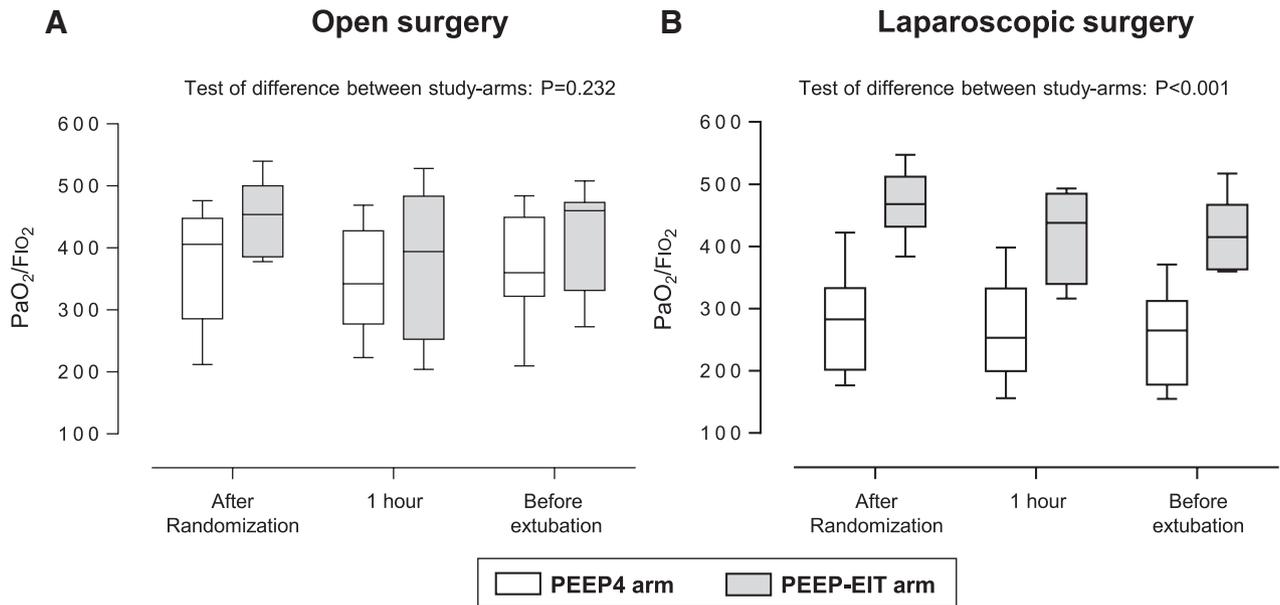


Fig. 8. Box plot (median with 25th and 75th percentiles) of PaO₂/F_iO₂ ratio during intraoperative period in open surgery (A) and laparoscopic surgery (B). Gray boxes represent positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT) arm, and white boxes represent PEEP of 4 cm H₂O (PEEP4) arm.

Table 4. Anesthetic Management and Outcomes

	PEEP4 (n = 20)	PEEP-EIT (n = 20)	P Value
Anesthetic management			
Length of anesthesia, median (IQ), min	235 (220–248)	205 (175–240)	0.013
Length of surgery, median (IQ), min	180 (158–195)	138 (115–168)	0.009
Urine output per hour, median (IQ), ml	141 (77–223)	139 (75–175)	0.683
Total fluids per hour, median (IQ), ml	552 (444–619)	667 (491–720)	0.175
Neuraxial anesthesia			
Intradural (%)	4 (20)	6 (30)	
Epidural (%)	3 (15)	3 (15)	
Vasoactive drug			
During recruitment maneuver (%)	16 (80)	15 (75)	
Continuous (%)	0 (0)	0 (0)	
Outcome			
Length of hospital stay, median (IQ), days	3 (2–3)	3 (2–3)	0.138
Computed tomography after extubation			
Time to computed tomography, median (IQ), min	50 (45–59)	55 (39–62)	

Data are expressed as median (IQ [interquartile range]) or number of patients (percent). P (Mann–Whitney test) for the difference between PEEP 4 and PEEP-EIT (laparoscopic and open surgery together). PEEP4, PEEP of 4 cm H₂O; PEEP-EIT, PEEP guided by electrical impedance tomography.

titration.²⁶ High PEEP might result in more hyperdistension than collapse whereas low PEEP might result in more collapse than hyperdistension. Our data suggest that an individually adjusted PEEP—providing the optimum compromise between lung collapse and hyperdistension—presents wide between-patient variability (from 6 to 16 cm H₂O). Recent trials individualizing PEEP during general anesthesia also showed wide variability.^{20,21,27} Such variability means that the use of a standardized PEEP for patients with “normal lungs” is problematic. For instance, when looking at our patients before randomization, when all were submitted to decremental PEEP titration, we observed that a fixed-PEEP

of 6 cm H₂O caused a wide range of lung collapse (from 3 to 33% of parenchymal collapse), whereas a fixed-PEEP of 16 cm H₂O caused 5 to 52% of parenchymal hyperdistension, with all of this variability depending exclusively on individual patient characteristics.

Some other aspects of this study are potentially relevant. We tested a method that has been shown to be fast (~5 min) and reproducible at the bedside.^{16,26} When PEEP challenges are performed in a decremental fashion and in small steps, the new equilibrium of imaging and mechanics is quickly achieved, within just three to five ventilation cycles. Thus, the complete lung response to each PEEP step

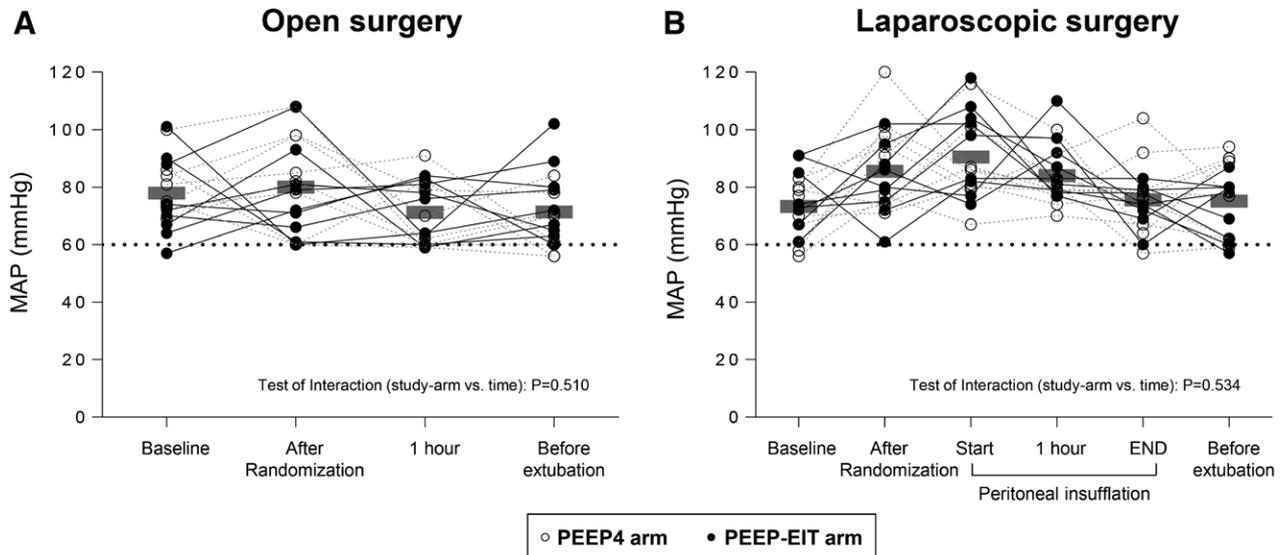


Fig. 9. Individual mean arterial pressure (MAP) and patients' mean during intraoperative period in open surgery (A) and laparoscopic surgery (B). Baseline was recorded after intubation. Closed circles represent patients ventilating under positive end-expiratory pressure titrated by electrical impedance tomography (PEEP-EIT), and open circles represent patients ventilating under positive end-expiratory pressure (PEEP) of 4 cm H₂O. There was no difference between groups in both types of surgery.

can be measured in just 20 to 30 s.¹⁶ In contrast, when using blood gases, the equilibrium takes 4 to 10 min,²⁸ which is impractical. Recently, a new approach using pulse-oximetry (which takes only 1 or 2 min for each step) was proposed.²¹ This procedure, however, could not offer any information about hyperdistension. In contrast, a key aspect of our EIT-based procedure is its high sensitivity to detect parenchymal hyperdistension or collapse,^{26,29} providing objective parameters to accomplish a dual target during PEEP titration: minimal postoperative collapse, as confirmed by computed tomography after extubation, and minimal hyperdistension, as suggested by lower ΔP and good hemodynamic tolerance.

Of note, we tested individual PEEP settings applied to two relevant populations of patients: open abdominal surgery and laparoscopic surgery. The PEEP titration procedure was applied after recruitment and homogenization of the lungs in both populations, demonstrating not only that anesthesia induction promotes massive lung collapse (despite the application of a standard PEEP of 4 cm H₂O), but also that an objective improvement in lung function can be achieved for these two populations, with long-lasting effects after surgery and minimal side effects.

Lung Injury and Postoperative Collapse

Patients undergoing laparoscopic surgery and ventilated at PEEP-EIT had ΔP consistently less than 12.5 cm H₂O, a threshold associated with a lower incidence of postoperative pulmonary complications.⁹ In contrast, patients allocated to PEEP4 frequently exceeded this threshold (fig. 7), thus being exposed to a higher risk of postoperative pulmonary complications.

We also demonstrated that optimal PEEP, compared with low fixed PEEP of 4 cm H₂O, not only reduces ΔP and improves compliance intraoperatively, but also reduces atelectasis in the postoperative period. The benefit is more profound for the patients in the laparoscopic than open surgery subgroup. Of note, in this study we did not evaluate the effect of the optimal intraoperative PEEP on the incidence and severity of postoperative pulmonary complications. In addition, the association of postoperative atelectasis with worse outcomes has not been a consensus.^{30,31} However, a fair majority of studies suggests that postoperation atelectasis is harmful. It can last for several days after surgery,³² increasing pulmonary complications, impairing respiratory function, and ultimately delaying patient discharge.^{31,33}

It is convenient, therefore, that a single ventilator adjustment, such as PEEP-EIT, minimized the two main factors implicated in perioperative complications without increasing length of hospital stay (fig. E5 in Supplemental Digital Content, <http://links.lww.com/ALN/B784>). Nevertheless, the hypothesis that individualized PEEP could produce better outcome remains to be proven and, if proven, the methods to titrate PEEP should be accessible at the bedside. Of note, in a recent trial,³⁴ an individualized PEEP followed by individualized continuous positive airway pressure postoperatively did not reduce the primary end point (a composite of postoperative pulmonary and systemic complications) when compared with a standard PEEP of 5 cm H₂O and oxygen therapy, but it did improve secondary outcomes.

PEEP and Body Mass Index

A significant correlation between optimum individual PEEP with body mass index was observed (fig. 3, $P < 0.001$),

although we noticed a wide variation, suggesting that the consideration of body mass index could not replace the physiologic individualization of PEEP.

Previous research has shown that, during the intraoperative period, atelectasis is positively correlated with body mass index.³⁵ Also, recent physiologic studies identifying “optimum” PEEP by sequential measurements of respiratory system compliance or deadspace during anesthesia consistently showed a higher PEEP requirement in obese patients.^{19,36} This higher PEEP requirement has been explained by increased pleural pressures during exhalation, strongly affected by the increased weight of chest-wall and abdominal structures.¹⁰ The increased weight, however, does not affect the intrinsic compliance of the chest wall, causing only a continuous offset of pleural pressures, thus generating “negative” transpulmonary pressures and favoring end-expiratory lung collapse.³⁷ Consequently, higher mean PEEP was required in our population to counterbalance the highest compressive forces in those patients with the highest body mass index, especially in those submitted to laparoscopic surgery (fig. 3).

This correlation between body mass index and PEEP-EIT also explains the strong correlation between the drop in ΔP (from baseline to PEEP-EIT) and body mass index (fig. 6). The higher the body mass index, the higher the pleural pressures and the higher the PEEP needed to counterbalance this offset in transpulmonary pressures. Interestingly, after overcoming this high pressure-offset with PEEP, not only the chest wall but also the lung compliance was preserved after recruitment and, consequently, ΔP at the PEEP-EIT were similar in the obese and slim patients (fig. E6 in Supplemental Digital Content, <http://links.lww.com/ALN/B784>). This explains why the most expressive drop in ΔP (up to 12 cm H₂O after PEEP-EIT; fig. 6) was found in the most obese: in these patients, the difference in respiratory-system compliance between PEEP4 (with very negative transpulmonary pressures and massive atelectasis) and PEEP-EIT was maximal.

Hemodynamics

When comparing study arms, there were no differences in arterial pressures, cardiac rate, or use of fluids or continuous vasoactive drugs during the intraoperative period. Despite the requirement of vasoactive agents during the recruitment maneuver in most patients, none needed it continuously, a result that is in line with previous studies.³⁸ A recent large, randomized, clinical trial³⁴ showed similar results, corroborating that recruitment maneuvers are safe and the use of individualized higher PEEP might not necessarily lead to hemodynamic instability or increased fluid administration. Multiple factors are associated with good hemodynamic tolerance, including previous optimization of fluids before the maneuvers,³⁸ use of pressure-controlled breaths for recruitment (instead of sustained pressures or continuous positive airway pressure),³⁹ and individualized PEEP, probably lowering pulmonary vascular resistance and preserving right ventricular function.⁴⁰

Study Limitations

The present study was a small, single-centered, physiologic proof-of-concept study, not powered to detect differences in hard outcomes. First, our number of patients was limited and heterogeneous. As expected, we did not detect significant differences in length of hospital stay or postoperative complications other than atelectasis. Second, our patients were graded American Society of Anesthesiologists Physical Status I or II. The use of recruitment maneuvers and titrated PEEP in more unstable patients was not tested and could increase the side effects of the strategy. Of note, a recent study testing an intensive recruiting strategy in vasoplegic patients after cardiac surgery³³ did not describe significant side effects. Third, the length of anesthesia and surgery were longer in the PEEP4 arm, which might have contributed to atelectasis formation in these patients. However, the computed tomography scan in this study was performed after extubation, and some patients might have performed uncontrolled recruitment maneuvers (by sighing or coughing), whereas others may have collapsed after falling asleep. Because most patients were fully awake during computed tomography, such confounding would only have decreased the chances of finding a significant difference in atelectasis. Performing computed tomography scans while patients were still under mechanical ventilation could have shown us the exact effect of PEEP, but it would not have provided the secondary outcome we were looking for (atelectasis after extubation). Fourth, the recruitment maneuver applied in this study lasted for 2 min. Because of the vasoplegia associated with anesthesia induction, many patients required vasoactive drugs during the first recruitment maneuver (table 4); in the second maneuver, however, such need was rare. It is possible that a shorter recruitment maneuver (15 to 30 s) might be used instead, showing preserved efficacy, but milder hemodynamic consequences as in a recent study.⁴¹ EIT was used to set PEEP according to lung hyperdistention and collapse. Titrating PEEP in a decremental way according to driving pressure might lead to similar results, though we did not test for this hypothesis.

Conclusions

Optimal PEEP values vary widely in healthy patients ventilated with protective V_T during general anesthesia for abdominal surgery. The application of the optimal PEEP obtained with EIT for each individual patient improves intraoperative oxygenation, lowers ΔP , and minimizes incidence and severity of postoperative atelectasis with minimal side effects. Large randomized trials should be conducted to determine the effect of physiologic tidal volume together with individualized optimal PEEP on the patient.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: mrotucci@gmail.com. Raw data available at: mrotucci@gmail.com.

Correspondence

Address correspondence to Dr. Tucci: Laboratório de Pneumologia LIM 09 Faculdade de Medicina da Universidade de São Paulo, Av. Doutor Arnaldo, 455 (Sala 2144, 2nd floor), São Paulo 01246-903, Brazil. mrotucci@gmail.com. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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