ANESTHESIOLOGY

Individualized *versus* Fixed Positive End-expiratory Pressure for Intraoperative Mechanical Ventilation in Obese Patients: A Secondary Analysis

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Optimal methods for preserving lung function in obese patients remain controversial.
- Previous studies in laparoscopic abdominal surgery have focused on the use of different levels of positive end-expiratory pressure (PEEP; either fixed or individualized based on measures of distribution of ventilation or lung compliance) with or without use of recruitment maneuvers.
- Electrical impedance tomography is a real time tool that allows visualization of distribution of ventilation and calculation of indices of regional inhomogeneity of ventilation, which may predict postoperative lung function.
- The authors combined the locally acquired data from two randomized controlled trials of such patients, an earlier physiologic study and a later subset of patients from a large multinational study (PROBESE) evaluating as a primary outcome oxygenation (Pa_{O_2}/F_{IO_2} ratio). They compared high or low fixed PEEP levels with or without recruitment and individualized PEEP using electrical impedance tomography.

What This Article Tells Us That Is New

- Individualized positive end-expiratory pressure (PEEP; median 18 cm H_2O) was superior to either fixed low levels (4 to 5 cm H_2O) or a higher level (12 cm H_2O with recruitment) with regards to oxygenation, driving pressures, and indices of regional ventilation.
- Despite improvement in lung function, no differences in postoperative pulmonary complications were observed. However, this cohort was not adequately powered for clinical outcomes.

ABSTRACT

Background: General anesthesia may cause atelectasis and deterioration in oxygenation in obese patients. The authors hypothesized that individualized positive end-expiratory pressure (PEEP) improves intraoperative oxygenation and ventilation distribution compared to fixed PEEP.

Methods: This secondary analysis included all obese patients recruited at University Hospital of Leipzig from the multicenter Protective Intraoperative Ventilation with Higher *versus* Lower Levels of Positive End-Expiratory Pressure in Obese Patients (PROBESE) trial (n = 42) and likewise all obese patients from a local single-center trial (n = 54). Inclusion criteria for both trials were elective laparoscopic abdominal surgery, body mass index greater than or equal to 35 kg/m^2, and Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score greater than or equal to 26. Patients were randomized to PEEP of 4 cm H_2O (n = 19) or a recruitment maneuver followed by PEEP of 12 cm H_2O (n = 21) in the PROBESE study. In the single-center study, they were randomized to PEEP of 5 cm H_2O (n = 25) or a recruitment maneuver followed by individualized PEEP (n = 25) determined by electrical impedance tomography. Primary endpoint was Pa_{O_2}/inspiratory oxygen fraction before extubation and secondary endpoints included intraoperative tidal volume distribution to dependent lung and driving pressure.

Results: Ninety patients were evaluated in three groups after combining the two lower PEEP groups. Median individualized PEEP was 18 (interquartile range, 16 to 22; range, 10 to 26) cm H_2O. Pa_{O_2}/inspiratory oxygen fraction before extubation was 515 (individual PEEP), 370 (fixed PEEP of 12 cm H_2O), and 305 (fixed PEEP of 4 to 5 cm H_2O) mmHg (difference to individualized PEEP, 145; 95% CI, 91 to 200; $P < 0.001$ for fixed PEEP of 12 cm H_2O and 210; 95% CI, 164 to 257; $P < 0.001$ for fixed PEEP of 4 to 5 cm H_2O). Intraoperative tidal volume in the dependent lung areas was 43.9% (individualized PEEP), 25.9% (fixed PEEP of 12 cm H_2O) and 26.8% (fixed PEEP of 4 to 5 cm H_2O) (difference to individualized PEEP: 18.0%; 95% CI, 8.0 to 20.7; $P < 0.001$ for fixed PEEP of 12 cm H_2O and 17.1%; 95% CI, 10.0 to 20.6; $P < 0.001$ for fixed PEEP of 4 to 5 cm H_2O). Mean intraoperative driving pressure was 9.8 cm H_2O (individualized PEEP), 14.4 cm H_2O (fixed PEEP of 12 cm H_2O), and 18.8 cm H_2O (fixed PEEP of 4 to 5 cm H_2O), $P < 0.001$.

Conclusions: This secondary analysis of obese patients undergoing laparoscopic surgery found better oxygenation, lower driving pressures, and redistribution of ventilation toward dependent lung areas measured by electrical impedance tomography using individualized PEEP. The impact on patient outcome remains unclear.

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General anesthesia with invasive ventilation can lead to the formation of atelectasis in the dependent lung, reduce end-expiratory lung volume, and impair arterial oxygenation[1] (more frequently in obese patients[2,3]), and may be exacerbated by pneumoperitoneum in laparoscopic surgery.[4] Atelectasis *per se* and the resulting overinflation of the remaining ventilated lung, as well as cyclic tidal recruitment and derecruitment, may contribute to postoperative pulmonary complications,[5] especially in obese patients,[6–8] and

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can lead to prolonged hospital stay[6] and increased mortality.[8,9] Atelectasis can be reopened using recruitment maneuvers[10,11] and can be kept open through adequate positive end-expiratory pressure (PEEP),[2,12] which may need to be higher in obese patients.[3,4,11,13] However, these measures may require increased infusion volumes and vasoactive medication doses.[14] Overall, low PEEP in obese patients is common,[15,16] and recruitment maneuvers are rarely used.[6]

Multiple methods exist to individualize PEEP. Optimization of compliance or oxygenation during PEEP titration maneuvers are common due to their simple execution. However, electrical impedance tomography can be used to optimize end-expiratory lung impedance,[17] regional pressure–volume curves,[18] or homogenization of tidal ventilation assessed during a standardized low-flow maneuver.[19] The regional ventilation delay index is a measure of regional ventilation distribution[19] and can be used to individualize PEEP to homogenize tidal ventilation and minimize atelectasis.[3]

A large multicenter, randomized trial (Protective Intraoperative Ventilation with Higher *versus* Lower Levels of Positive End-Expiratory Pressure in Obese Patients [PROBESE]) pragmatically compared a fixed PEEP of 12 cm H_2O and hourly repeated recruitment maneuvers with a PEEP of 4 cm H_2O in more than 2,000 obese patients during general anesthesia.[20] Although differences in postoperative pulmonary complications between groups were not statistically significant, fixed high PEEP resulted in better intraoperative lung function parameters.[20] In a previous single-center study in obese patients undergoing laparoscopic abdominal surgery, the electrical impedance tomography method described above revealed a large range of optimal PEEP values between 10 and 26 cm H_2O with a mean PEEP value of 18 cm H_2O.[3] It remains unclear whether individualized PEEP settings as compared with a higher fixed PEEP would be advantageous regarding intraoperative oxygenation and ventilation distribution.

We therefore tested the hypothesis that individualized PEEP titration improves oxygenation and better restores ventilation distribution to the dependent lung than fixed PEEP values of 4 to 5 or 12 cm H_2O. To do so, we compared all PROBESE patients that were recruited at the University of Leipzig Medical Center (Germany) with all patients from our previously published single-center study,[3] while retaining Pa_{O_2}/inspiratory oxygen fraction (F_{IO_2}) as the primary endpoint according to the original study design of the single-center study. However, Pa_{O_2}/F_{IO_2} proved to be of limited clinical value as a surrogate for postoperative patient outcomes. Recently, there has been increasing evidence that alterations in lung physiology and respiratory system mechanics may be linked more closely to patient outcome. Therefore, in this secondary analysis, we included intraoperative ventilation distribution measured by electrical impedance tomography and parameters of intraoperative lung mechanics (dynamic compliance and driving pressure) as additional secondary endpoints.

Materials and Methods

This analysis included all obese patients of a previous single-center study[3] (German Clinical Trials Register: No. DRKS00004199, www.who.int/ictrp/network/drks2/en/) and all patients included in the PROBESE multicenter trial (ClinicalTrials.gov No. NCT02148692, https://clinicaltrials.gov/ct2/show/NCT02148692) from the University of Leipzig Medical Center (Germany). Approvals for both trials were granted by the Leipzig University Ethics Committee (No. 334/16-lk; No. 196-11-ff-8042011). Prospective electrical impedance tomography measurements were performed on the PROBESE patients to facilitate the comparison presented here, for which we obtained an addendum from the local ethics committee before the start of patient recruitment of the PROBESE study at our center. All patients gave written informed consent before inclusion. Detailed descriptions of the methods and the study protocols of both studies were recently published elsewhere,[3,20,21] and the original protocols are available in Supplemental Digital Content 1 (http://links.lww.com/ALN/C578) and Supplemental Digital Content 2 (http://links.lww.com/ALN/C579).

Patients

Patients were recruited between November 2012 and July 2013 for our single-center trial (n = 54) and between October 2016 and January 2018 for the PROBESE trial (whole study, n = 2,013; at the Leipzig site, n = 42; fig. 1). Both trials included obese patients with a body mass index

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greater than or equal to 35 kg/m^2, age greater than or equal to 18 yr, and a medium or high risk of postoperative pulmonary complications (Assess Respiratory Risk in Surgical Patients in Catalonia [ARISCAT] score greater than or equal to 26)[22] scheduled for elective abdominal surgery.

Both in the single-center and PROBESE trials, patients were randomized to an intervention and a control group. The intervention group received a recruitment maneuver followed by either individualized PEEP (single-center trial) or a fixed PEEP of 12 cm H_2O (PROBESE trial). Patients of the control group received PEEP of 5 cm H_2O (single-center trial) or 4 cm H_2O (PROBESE trial), and in the current analysis, they are combined in one "low PEEP" group (fixed PEEP of 4 to 5 cm H_2O).

Anesthesia

All patients received a standardized infusion of crystalloid fluid and total intravenous anesthesia with propofol and remifentanil (all patients in the single-center trial; two patients in the PROBESE trial) or balanced anesthesia with desflurane/sevoflurane and sufentanil/remifentanil (38 patients in the PROBESE trial).[3,21] Routine perioperative monitoring included measurement of invasive arterial blood pressure.

Protocol

Interventions. Constant-flow, volume-controlled mechanical ventilation was provided by an intensive care ventilator (EVITA-XL; Dräger Medical AG, Germany) with a tidal volume (V_T) of 7 ml/kg predicted body weight in the PROBESE trial and 8 ml/kg predicted body weight in the single-center trial. F_{IO_2} was set to 0.4 or higher if necessary to achieve a target oxygen saturation measured by pulse oximetry greater than or equal to 92% in both trials. The initial respiratory rate was set to 12 breaths per minute. The inspiratory-to-expiratory ratio and inspiratory time were set to achieve end-inspiratory and end-expiratory zero flow with inspiratory pause. During anesthesia, respiratory rate, inspiratory flow, and inspiratory-to-expiratory ratio were adjusted as required to maintain normocapnia (Pa_{CO_2} greater than or equal to 35 and less than or equal to 45 mmHg).

Timing of measurements, ventilation and PEEP setting, and the positioning of all patients are illustrated in figure 2. All patients in the PROBESE trial at the University of Leipzig Medical Center prospectively received additional electrical impedance tomography measurements at time points to coincide with the single-center trial. Electrical impedance tomography recordings were performed before induction of anesthesia and 2 h after extubation; arterial

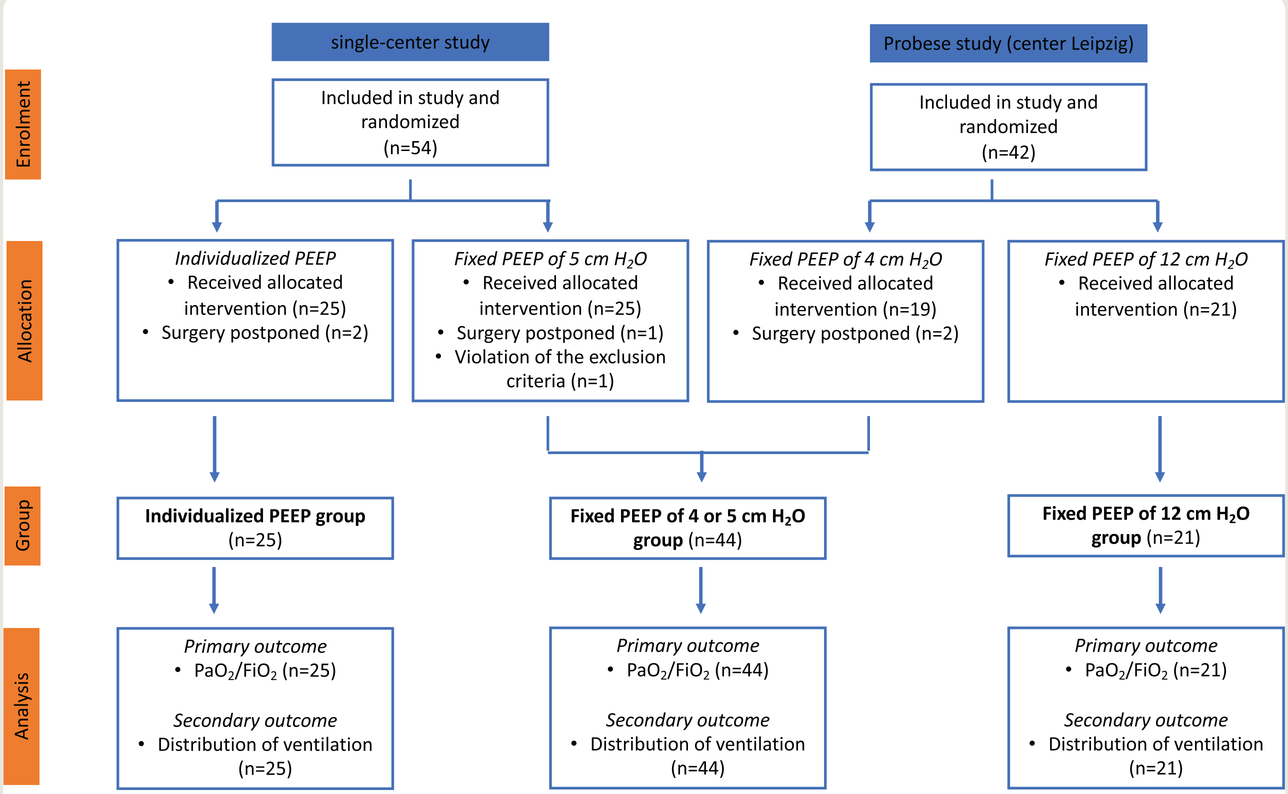

Fig. 1. Flowchart of enrollment and outcomes, end-expiratory lung volume. F_{IO_2} was adjusted to achieve a target oxygen saturation measured by pulse oximetry greater than or equal to 92% in both trials. F_{IO_2}, fraction of inspired oxygen; Pa_{O_2}, partial pressure of oxygen in arterial blood; PEEP, positive end-expiratory pressure.

blood gas analysis and electrical impedance tomography data were measured in the spontaneously breathing patient at ambient air pressure. After induction of anesthesia, baseline measurements were performed in all patients 10 min after the start of mechanical ventilation at a PEEP of 4 or 5 cm H_2O. After the last measurement point, F_{IO_2} was set to 1.0 before extubation according to current clinical standards.

Study Groups. The patients randomized to control groups remained at fixed PEEP of 4 to 5 cm H_2O without receiving recruitment maneuvers at any time.[3,21]

According to the PROBESE protocol, patients randomized to the fixed PEEP of 12 cm H_2O group received recruitment maneuvers (inspiration-to-expiration ratio, 1:1; PEEP, 12 cm H_2O; respiratory rate, 6 breaths per minute; increasing V_T in steps of 4 ml/kg of predicted body weight until plateau pressure reaches 40 cm H_2O followed by three breaths while maintaining plateau pressure of 40 to 50 cm H_2O) after tracheal intubation (and after ventilator disconnection) and hourly throughout mechanical ventilation.[3]

The individualized PEEP group received a recruitment maneuver (inspiration-to-expiration ratio, 1:1; peak pressure, 50 cm H_2O; PEEP, 30 cm H_2O; respiratory rate, 6 breaths per minute) for 10 breaths followed by a unique decremental PEEP titration before the start of surgery and before insufflation of pneumoperitoneum. Starting with a PEEP of 26 cm H_2O and descending in steps of 2 cm H_2O to a PEEP of 4 cm H_2O, the regional ventilation delay index was calculated at every PEEP step, and the PEEP value corresponding to the lowest value of regional ventilation delay index was identified as individual best PEEP,[3,19,23] which was maintained throughout mechanical ventilation. An additional recruitment maneuver was performed immediately before extubation at the end of the surgical procedure.[3]

Hypotension was defined as mean arterial pressure less than 60 mmHg. Because we wanted to exclude possible confounding effects on pulmonary circulation, norepinephrine was the only vasopressor applied for treating hypotension. Bradycardic episodes during the recruitment maneuver were exclusively treated with atropine.

Electrical Impedance Tomography. Electrical impedance tomography monitoring consists of an electrode belt containing 16 or 32 electrodes that is placed around the chest cranial to the diaphragm at the height of the third to fourth intercostal space. An alternating current (typically 5 mA at a frequency of 50 kHz) is applied to a first pair of electrodes, and the resulting surface potentials are registered in the remaining electrode pairs. Subsequently, the location of

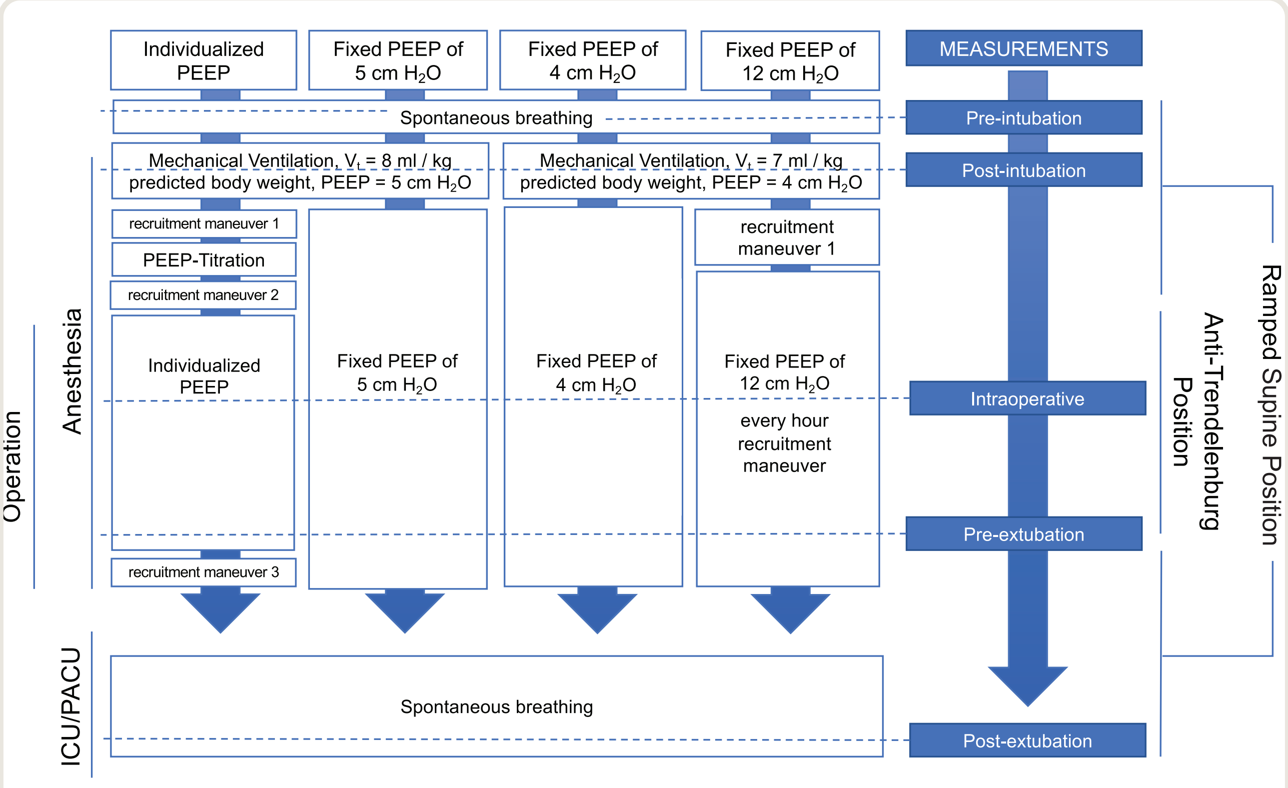

Fig. 2. Schematic diagram of study protocol and interventions for all groups. ICU, intensive care unit; PACU, postanesthesia care unit; PEEP, positive end-expiratory pressure.

the current injection and voltage measurements is rotated continuously around the chest. Thus, a complete rotation of the injecting electrode pair results in a total of 208 voltage measurements when using a 16-electrode belt. Impedance of the tissue passed by the current is calculated using the Ohm law. After algorithm-based reconstruction, a two-dimensional, real-time, cross-sectional image of pulmonary ventilation is displayed on a monitor. Changes in relative impedance during a respiratory cycle are displayed using a white to dark blue color scheme (with darker color tones of blue indicating a decrease in impedance, which is to be equated with a decrease in regional ventilation).

For electrical impedance tomography–based individualization of PEEP in the single-center study, the regional ventilation delay for each pixel in the electrical impedance tomography image was determined during a standardized low-flow maneuver of 12 ml/kg predicted body weight, and the regional ventilatory delay index was then defined as the SD for all pixels' regional ventilatory delay. The lower the regional ventilation delay index, the more homogeneous the regional ventilation of the lung with reduction of overdistention as well as atelectasis formation. The PEEP corresponding to the lowest regional ventilatory delay index was set as individualized PEEP (method described earlier in Nestler *et al.* including its supplement[3]; see also Muders *et al.*[19]).

Measurements. Ventilation parameters were recorded by the display of the mechanical ventilator. Blood gases, lactate, and pH were determined immediately after sampling with a standard blood gas analyzer (ABL 800; Radiometer, Denmark). Ventilation distribution images were obtained with a commercially available electrical impedance tomography system (PulmoVista 500; Dräger Medical AG). Tidal distributions of ventilation to dependent and nondependent lung zones[24] were quantified offline using the commercially available Dräger electrical impedance tomography analysis tool (version 6.1; Dräger Medical AG) and customized institutional software. The ratio of dependent to nondependent ventilation is provided.

Statistics

The analysis and statistical plan were conceived after the data were accessed. However, the plan to carry out this secondary analysis was documented before inclusion of local patients in the PROBESE trial after discussing it with the steering committee and arranging for the electrical impedance tomography measurements. Visual inspection of the primary variables was performed to detect potential differences between the low PEEP group from the PROBESE and the single-center trial. Given this inspection, the similarities in trial design and inclusion criteria, the small time difference between patient recruitment, and the study team being the same, the assumption was made that the local site data from the trials can be pooled. The primary endpoint Pa_{O_2}/F_{IO_2} immediately before extubation was adopted from the single-center study (registered in 2012) and chosen for comparability between the primary analysis and the current subanalysis. Further endpoints are intraoperative percentage of V_T to nondependent/dependent lung, which is the percentage of the tidal ventilation of the dependent lung in relation to total ventilated lung area as defined in Mauri *et al.*,[24] and the ventilatory ratio, which divides the measured by the expected product of minute ventilation and Pa_{CO_2} as defined in Sinha *et al.*[25]

With the observed SDs for the individualized PEEP group of the single-center study being 10.2 percentage points for ventilation distribution and 85.5 mmHg for Pa_{O_2}/F_{IO_2}, the current analysis would have 80% power in detecting a difference of 10.0 percentage points and 11.2 kPa, respectively, compared to the fixed PEEP of the 12 cm H_2O group. These estimates use a significance level of 2.5% for Bonferroni correction.

Differences between groups at a prespecified point in time were compared with a linear model with the baseline value as a covariate and a Bonferroni correction for multiple groups. For these models, a Wald CI was used, and the P value corresponded to it. In data with heavily skewed distributions, group comparisons were made using a Kruskal–Wallis test. For repeated measures analyses, a mixed effects model was used, optimizing the restricted maximum likelihood (using the lme4 package[26]), which will provide unbiased estimates despite missing data, assuming that they are "missing at random." Patient was taken as the random term with group and time including their interaction as fixed effects. A type two ANOVA was performed with a Wald chi-square test using the default settings from the "Anova" command for the "mer" class from the "car" package.[27] Differences in categorical variables were assessed by the chi-square test. For analysis of ventilation distribution at different PEEP levels during the titration process, a paired t test with Bonferroni correction was used. The association between continuous variables is assessed with linear correlation, where the CI is based on Fisher z transformation. Comparison of two dependent correlations was performed with the Zou method from the "cocor" package.[28,29] All statistical analyses were performed using R Version 3.6.1 (RStudio, Version 1.2.1335, http://www.R-project.org/; R Foundation for Statistical Computing, Austria). Summary statistics are presented as mean ± SD, all tests were two-tailed, and $P < 0.05$ was considered to be statistically significant.

Results

Study Population

A total of 90 patients were included in this analysis: 50 patients from the single-center trial[3] and 40 patients from the PROBESE trial.[20] The patients were categorized into three different groups subject to their random allocation in the initial clinical trials: fixed PEEP of 4 to 5 cm H_2O

(44 patients), individualized PEEP (25 patients), and fixed PEEP of 12 cm H_2O (21 patients). Visual inspection did not indicate any relevant differences in important variables between the low PEEP groups from the PROBESE and single-center trials. The patient flow (fig. 1) demonstrates that all patients who underwent surgery were included in the analysis of the primary outcome and that the intended intervention was provided to each of these patients. Their baseline characteristics are listed in table 1.

Seventy-three patients underwent a gastric bypass surgery, 16 patients had a sleeve gastrectomy (nine from the fixed PEEP of 4 to 5 cm H_2O, two from the individualized PEEP, and five from the fixed PEEP of 12 cm H_2O group), and one patient from the fixed PEEP of 4 to 5 cm H_2O group had rectal cancer surgery. All surgeries were performed laparoscopically and lasted for a mean ± SD of 173 ± 36, 128 ± 42, and 143 ± 47 min in the individualized PEEP, fixed PEEP of 12 cm H_2O, and fixed PEEP of 4 to 5 cm H_2O groups, respectively. Surgery was performed in the reverse Trendelenburg position, with exception of the patient who received rectal cancer surgery in the Trendelenburg position. The intraoperative characteristics provided in table 2 show that titration of individualized PEEP led to an average PEEP of 18.5 cm H_2O (median, 18 [interquartile range, 16 to 22; range, 10 to 26 cm H_2O]).[3] The body mass index in the individualized PEEP ranged from 38.1 to 65.1 kg/m^2, and the supplement in the single-center trial[3] shows that the correlation between optimal PEEP and body mass index is too weak to use body mass index for choosing a PEEP value.

Respiratory Outcomes

In the primary variables, a small number of data are missing for technical reasons (fig. 3). The Pa_{O_2}/F_{IO_2} ratio before tracheal extubation was 515.3 mmHg in the individualized PEEP group, 369.8 mmHg in the fixed PEEP of 12 cm H_2O group, and 304.5 mmHg in the fixed PEEP of 4 to 5 cm H_2O group. The difference to the individualized PEEP group was 145.5 mmHg ([95% CI, 90.9 to 200.4 mmHg; $P < 0.001$] fixed PEEP of 12 cm H_2O) and 210.8 mmHg ([95% CI, 164.5 to 257.6 mmHg; $P < 0.001$] fixed PEEP of 4 to 5 cm H_2O]). Figure 3A depicts the course of Pa_{O_2}/F_{IO_2} through time. After extubation, the differences between the groups vanished.

The individualized PEEP group also showed better respiratory system mechanics as indicated by lower driving pressure and, thus, higher dynamic compliance (table 2; fig. 3B). Notably, Pa_{CO_2} and end-tidal partial pressure of carbon dioxide do not differ significantly between groups. The ventilatory ratio increased during the course of the operation, but did not differ between the groups.

Distribution of Ventilation

Induction of anesthesia and mechanical ventilation shifted regional distribution of V_T to the nondependent lung, which could be reversed in the individualized PEEP group, but remained almost unchanged in both fixed PEEP groups until patients returned to spontaneous breathing (fig. 3C). Intraoperatively, the percentage V_T in the dependent lung was 43.9% in the individualized PEEP group. It was 25.9% in the fixed PEEP of 12 cm H_2O group (difference to individualized PEEP, 18% [95% CI, 8.0 to 20.7]; $P < 0.001$) and 26.8% in the fixed PEEP of 4 to 5 cm H_2O group (difference to individualized PEEP, 17.1% [95% CI, 10.0 to 20.6]; $P < 0.001$).

Intraindividual Distribution of Ventilation

At each PEEP titration stage in the individualized PEEP group, electrical impedance tomography measurements

Table 1. Patient Characteristics

	Fixed PEEP of 4 to 5 cm H_2O (n = 44)	Fixed PEEP of 12 cm H_2O (n = 21)	Individualized PEEP (n = 25)
Female, No. (%)	29 (66)	15 (71)	17 (68)
Age, yr	46.5 ± 14.1	43.6 ± 11.3	44.9 ± 10.3
< 45, No. (%)	21 (48)	11 (52)	11 (44)
Height, cm	171 ± 11.9	169 ± 8.7	173 ± 10.7
Body mass index, kg/m^2	51.0 ± 9.5	51.4 ± 13.4	48.2 ± 7.0
Assess Respiratory Risk in Surgical Patients in Catalonia score*	35.0 ± 6.0	33.5 ± 5.5	33.4 ± 4.6
> 44, No. (%)	5 (12)	2 (10)	1 (4)
Smoking status,† No. (%)			
Never	24 (57)	11 (61)	12 (48)
Former	10 (24)	7 (39)	5 (20)
Current	8 (19)	0 (0)	8 (32)

Entries are mean ± SD or No. (%).
*One value missing (fixed PEEP of 4 to 5 cm H_2O). †Five values missing (two in fixed PEEP of 4 to 5 cm H_2O group, three in fixed PEEP of 12 cm H_2O group).
PEEP, positive end-expiratory pressure.

Table 2. Intraoperative Respiratory Parameter during Mechanical Ventilation

	Fixed PEEP of 4 to 5 cm H_2O (n = 44)			Fixed PEEP of 12 cm H_2O (n = 21)			Individualized PEEP (n = 25)			
	After Intubation	Intraoperative	Before Extubation	After Intubation	Intraoperative	Before Extubation	After Intubation	Intraoperative	Before Extubation	*P* Value
Tidal volume, ml	476 ± 92	476 ± 92	481 ± 96	443 ± 77	435 ± 65	424 ± 61	525 ± 93	526 ± 91	532 ± 94	0.003
Tidal volume/predicted body weight, ml/kg	7.26 ± 0.47	7.26 ± 0.36	7.27 ± 0.35	7.16 ± 0.42	7.03 ± 0.17	6.91 ± 0.26	7.50 ± 0.29	7.51 ± 0.28	7.53 ± 0.29	—
PEEP, cm H_2O	4.6 ± 0.5	4.6 ± 0.5	4.6 ± 0.5	4.8 ± 2.4	12 ± 0	12 ± 0	5 ± 0	18.5 ± 4.6	18.5 ± 4.6	< 0.001
Peak pressure, cm H_2O	23.5 ± 4.8	28.0 ± 4.1	25.2 ± 4.1	23.7 ± 6.9	29.0 ± 4.8	27.6 ± 3.3	26.1 ± 5.4	33.8 ± 5.6	31.7 ± 6.5	< 0.001
Plateau pressure, cm H_2O	17.9 ± 3.9	23.4 ± 3.9	21.1v5.2	21.8 ± 7.1	26.4 ± 5.1	25.5 ± 5.2	19.6 ± 4.7	28.3 ± 4.6	25.6 ± 5.1	< 0.001
Driving pressure, cm H_2O	13.3 ± 4.1	18.8 ± 4.1	16.5 ± 5.5	16.9 ± 7.6	14.4 ± 5.1	13.5 ± 5.2	14.6 ± 4.7	9.8 ± 1.4	7.1 ± 1.4	< 0.001
Dynamic compliance, ml/cm H_2O	39.4 ± 14.1	26.6 ± 7.9	32.6 ± 12.0	30.3 ± 13.1	32.8 ± 10.0	30.2 ± 7.2	40.2 ± 12.3	55.1 ± 12.5	79.9 ± 18.9	< 0.001
Pao_2/Fio_2, mmHg	305 ± 115	325 ± 110	327 ± 118	261 ± 101	397 ± 109	371 ± 106	260 ± 127	485 ± 80	515 ± 86	< 0.001
$Paco_2$, mmHg	41.0 ± 4.9	45.4 ± 5.2	46.0 ± 6.0	42.7 ± 6.7	44.9 ± 4.1	48.8 ± 6.4	40.5 ± 5.1	44.6 ± 2.0	43.3 ± 3.1	0.099*
$Petco_2$, mmHg	37.9 ± 6.3	39.1 ± 5.3	40.5 ± 6.2	37.7 ± 5.8	42.3 ± 2.3	44.2 ± 4.3	41.0 ± 10.1	42.0 ± 9.5	40.9 ± 4.7	0.169*
Respiratory rate, breaths/min	12.9 ± 1.5	16.3 ± 2.6	17.7 ± 2.8	12.2 ± 0.7	16.5 ± 2.7	18.5 ± 2.9	12.3 ± 1.2	15.7 ± 3.3	16.3 ± 2.9	0.204
Minute ventilation (l/min)	6.1 ± 1.2	7.6 ± 1.3	8.4 ± 1.3	5.4 ± 1.2	7.2 ± 1.4	7.8 ± 1.4	6.5 ± 1.1	8.1 ± 1.4	8.5 ± 1.4	0.028
Ventilatory ratio	1.02 ± 0.20	1.40 ± 0.32	1.57 ± 0.36	0.99 ± 0.16	1.39 ± 0.24	1.67 ± 0.41	1.00 ± 0.16	1.36 ± 0.29	1.39 ± 0.27	0.438*

Gas volumes are given in body temperature and pressure saturated conditions. Note that tidal volume/predicted body weight was prescribed and cannot be tested statistically. Entries are the mean ± SD, and *P* values compare the three arms from a repeated-measures ANOVA.

*Evidence for an interaction between group and time.

PEEP, positive end-expiratory pressure; $Petco_2$, end-tidal partial pressure of carbon dioxide.

were performed. Thus, it is possible to provide values at each PEEP level. Figure 4 shows that the mean V_T percentage in the dependent lung was 9.7 percentage points (95% CI, 6.9 to 12.7; $P < 0.001$) lower at a PEEP of 4 cm H_2O compared to 12 cm H_2O, which was, in turn, 11.3 points (95% CI, 7.9 to 14.8; $P < 0.001$) lower compared with the individualized PEEP setting.

Correlation between Electrical Impedance Tomography and Ventilatory Ratio or Oxygenation

The linear correlation coefficient between regional distribution of V_T and the ventilatory ratio was −0.08 (95% CI, −0.31 to 0.16; $P = 0.496$) and was −0.51 (95% CI, −0.67 to −0.31; $P < 0.001$) between regional distribution of V_T and Pao_2/Fio_2. The difference between the two correlation coefficients is 0.43 (95% CI, 0.10 to 0.73; $P = 0.010$). In a linear regression model, Pao_2/Fio_2 decreased by 51.8 mmHg for every 10 percentage points change in regional distribution of V_T. Furthermore, there was a strong inverse correlation between driving pressure and Pao_2/Fio_2, with a linear correlation coefficient of −0.68 (95% CI, −0.79 to −0.53; $P < 0.001$).

Patient Safety

Basic hemodynamic data and a list of the complications by treatment arm are provided in table 3. During anesthesia and surgery, a considerable number of patients in all three arms had arterial hypotension and required vasopressors (in all cases, norepinephrine only) despite crystalloid fluid infusion of about 4 ml · kg^{-1} · h^{-1}, with a slightly—but significantly—larger infusion rate in the individualized PEEP arm (table 3). The number of patients requiring continuous norepinephrine infusion did not significantly differ between groups ($P = 0.764$), and overall rates were low. Moreover, 80% of patients in the individualized PEEP, 86% in the fixed PEEP of 12 cm H_2O, and 89% in the fixed PEEP of 4 to 5 cm H_2O groups also received boluses of vasoactive injections during anesthesia outside the recruitment maneuvers ($P = 0.585$). The bolus equivalents differed significantly between the groups ($P = 0.017$), but were low overall. The course of lactate was significantly lower in the individualized PEEP group ($P = 0.007$), but we did not observe differences in the course of base excess, nor did we observe any signs of cardiovascular insufficiency or shock. During recruitment maneuvers, almost all of the individualized PEEP patients (92%) but only half of the fixed PEEP of 12 cm H_2O patients (48%) required vasoactive medication.

Discussion

We showed that for obese patients undergoing laparoscopic surgery, recruitment maneuver followed by electrical impedance tomography–guided individualized PEEP resulted in (1) higher PEEP, (2) better arterial oxygenation, (3) lower driving pressures, and (4) redistribution of ventilation to

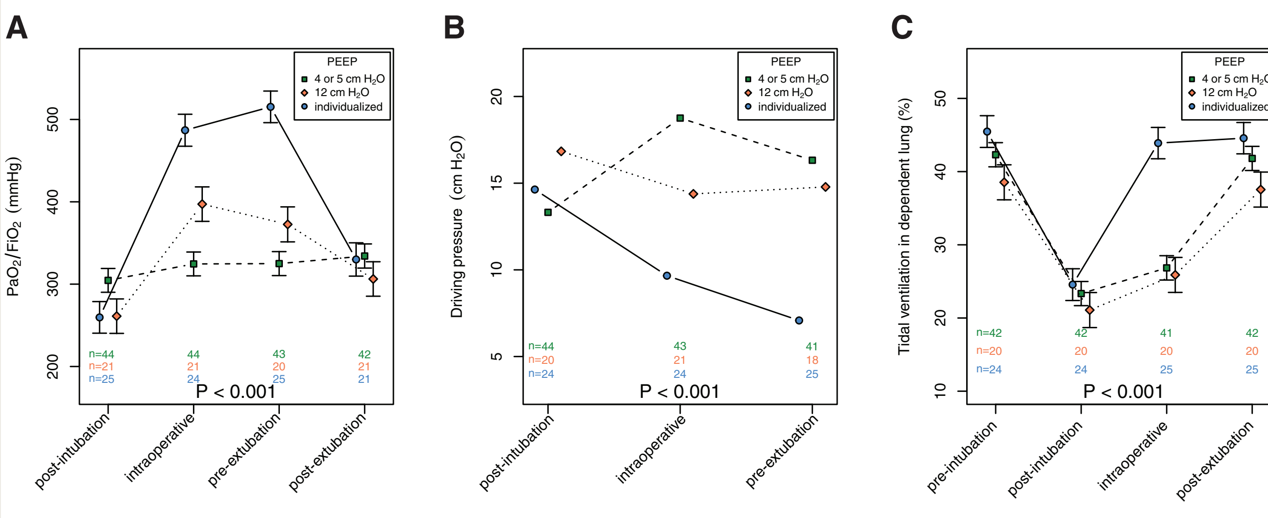

Fig. 3. Time course of Pao_2/Fio_2 (mmHg) (*A*), driving pressure during mechanical ventilation (cm H_2O) (*B*), and distribution of regional ventilation of tidal volume (V_T) distributed to the nondependent lung calculated from electrical impedance tomography (%) (*C*). *Points* represent estimated means, and *whiskers* indicate the standard errors from the linear mixed models. The intraoperative measurement point was made 30 min before the estimated end of the surgical procedure. The arterial blood gas analysis for measurement of Pao_2/Fio_2 was obtained after a 3-min period with an Fio_2 of 1.0. Fio_2, fraction of inspired oxygen; Pao_2, partial pressure of oxygen in arterial blood; PEEP, positive end-expiratory pressure.

dependent lung areas, when compared with recruitment maneuver followed by a fixed PEEP of 12 cm H_2O or low PEEP of 4 or 5 cm H_2O without recruitment maneuver. Taken together and considering indicators of dead space and overdistention, these findings strongly suggest that individually titrated PEEP values further reduce atelectasis formation in dependent lung areas as compared with both groups of the PROBESE study, which used a pragmatic approach comparing lower and higher fixed PEEPs not necessarily aiming for full lung recruitment.[20] Changes in end-expiratory lung volume previously reported in the patients from the single-center trial provide evidence that atelectasis occurs at lower PEEP.[3] Lung recruitment potential above a PEEP of 12 cm H_2O is confirmed by intraindividual comparisons of regional ventilation distribution in the individualized PEEP subgroup (fig. 4), showing significantly higher ventilation of the dependent lung with individualized PEEP. The difference between the fixed PEEP of 4 cm H_2O and the fixed PEEP of 12 cm H_2O arms in driving pressure before extubation in our local subgroup was comparable to that of the whole PROBESE trial (−6.6 *vs.* −5.6 cm H_2O, respectively), suggesting that the effects we observed locally might be representative of the whole study population. This implies that a recruitment maneuver followed by a high PEEP of 12 cm H_2O is not sufficient to recruit the lung completely, at least for some of the patients.

Measurements of regional ventilation by electrical impedance tomography during a low-flow breath show delayed filling of (mainly dependent) lung areas if PEEP is set below the closing pressure of those lung units.[20,23] If airway pressure exceeds the opening pressure of the collapsed lung unit during the low-flow breath, a delayed change in local impedance (ventilation) can be detected by electrical impedance tomography. Minimizing this temporal inhomogeneity of regional ventilation by setting PEEP according to the regional ventilation delay index approach[3,20,23] should thus result in the lowest PEEP that minimizes tidal alveolar collapse. Recent experimental evidence demonstrates that the regional ventilation delay index approach improves the ventilation/perfusion ratio with a lower PEEP than PEEP optimization using an open-lung approach based on highest oxygenation.[30] In the single-center study,[3] individualized PEEP determined by this regional ventilation delay index approach resulted in PEEP values of 10 to 26 (median, 18) cm H_2O, which were significantly higher than the 12 cm H_2O used in the PROBESE study.[20] Other studies in bariatric surgery using other optimization parameters regularly found PEEP levels greater than 15 cm H_2O.[12,31] In laparoscopic nonobese patients, mean PEEP was about 15 cm H_2O.[32] Our findings are in line with a recently published study by Tharp *et al.*[4] that showed a correlation between optimal PEEP and patient body mass index, but also found that body mass index could not be used to prescribe PEEP, further highlighting the need for individualized ventilation in this specific patient group. Practical issues that may hinder the application of an electrical impedance tomography–based PEEP strategy in the operating room include the limited availability of electrical impedance tomography and the fact that some anesthesia machines may not allow PEEP values greater than 20 cm H_2O.

Recruitment maneuvers are frequently used to apply high pressures to the lung tissue and may themselves contribute to ventilator-associated lung injury.[33] However, the

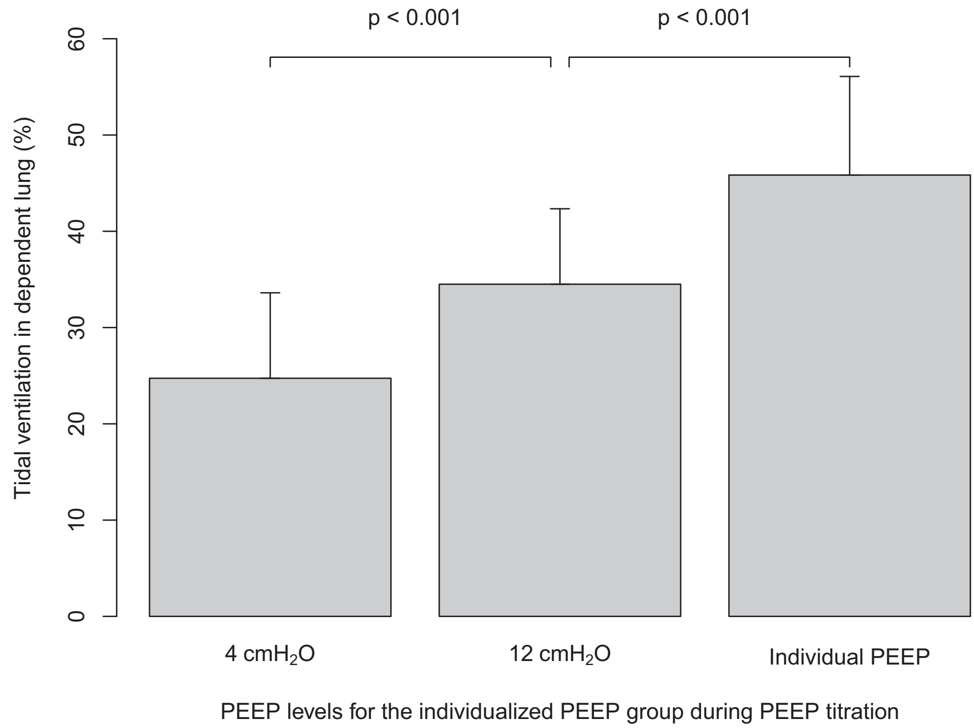

Fig. 4. Intraindividual comparison of the percentage tidal volume in the dependent lung at different PEEP titration stages in the individualized PEEP group calculated from electrical impedance tomography. *Whiskers* represent SDs. PEEP, positive end-expiratory pressure.

intraoperative improvements in the individualized PEEP group were achieved without repetitive intraoperative recruitment maneuvers[3] as performed in the PROBESE trial.[20] An intraoperative repetition of recruitment maneuvers does not improve gas exchange and lung function[34]; for patients with mainly primary pulmonary acute respiratory distress syndrome (ARDS), it is critical[35] and may additionally lead to severe hemodynamic compromise.

Individualized PEEP was associated with better respiratory system mechanics compared with a fixed PEEP, regardless of whether it was 4, 5, or 12 cm H_2O. The parameters indicating this were better distribution of gas to dependent lung areas, lower driving pressures, and higher oxygenation. The ventilatory ratio suggests that there was a change in neither overdistention nor dead space ventilation. Moreover, there was no correlation between distribution of ventilation and ventilation ratio, but there was a correlation between distribution of ventilation and oxygenation. This supports the notion of higher ventilation without an increase in dead space. The significantly higher driving pressure of both the fixed PEEP of 4 to 5 cm H_2O and fixed PEEP of 12 cm H_2O groups may contribute to increased postoperative pulmonary complications.[36] Note that there was a small difference in intraoperative tidal volumes between groups, which is due to the fact that different, but fixed, tidal volumes were prescribed in the two studies (7 ml/kg predicted body weight in the PROBESE study *vs.* 8 ml/kg predicted body weight in the single-center study). However, we do not expect this to be clinically relevant with regard to postoperative pulmonary complications, as these tidal volumes agree with the concept of modern lung protective ventilation strategies,[37] and even higher tidal volumes up to 10 ml/kg do not lead to more frequent occurrence of postoperative pulmonary complications.[38]

The large PROBESE trial could not confirm the hypothesis that a ventilation approach with a higher PEEP of 12 cm H_2O and recruitment maneuvers reduced postoperative pulmonary complications, despite reduction in driving pressures.[20] This seems to be in contrast to patients with ARDS, where lower driving pressures proved to be associated with improved outcome.[39,40] However, the relative risks in the ARDS studies would have equated to a risk difference of fewer than 3 percentage points given the observed driving pressures in PROBESE, and the study was not powered to detect such small differences. It is quite conceivable that individualized PEEP, which leads to lower driving pressures, might have greater impact on clinical outcome.

The lack of difference in postoperative pulmonary complications between high and low PEEP groups in the PROBESE trial may be partially explained by our consistent observations that lung recruitment associated with higher PEEP in obese patients was not preserved after tracheal extubation (fig. 3, A

Table 3. Vital Parameters, Vasoactive Medication, and Complications during and after Surgery

	Fixed PEEP of 4 to 5 cm H_2O (n = 44)	Fixed PEEP of 12 cm H_2O (n = 21)	Individualized PEEP (n = 25)	*P* Value
During surgery				
Heart rate, beats/min	65 ± 12	67 ± 13	69 ± 12	0.060
Mean arterial blood pressure, mmHg	73 ± 13	79 ± 11	77 ± 14	0.078
Lactate, mmol/l	0.87 ± 0.30	0.91 ± 0.26	0.71 ± 0.22	0.007
Base excess, mmol/l	−1.5 ± 2.7	−2.2 ± 2.2	−2.1 ± 2.7	0.442
Total fluid infusion rate, ml · h^{-1} · kg^{-1}	3.5 ± 1.1	3.7 ± 1.3	4.2 ± 1.0	0.028
Bradycardia (< 50 beats/min), during recruitment maneuvers	—	7 (33)	7 (28)	0.755
Bradycardia (< 50 beats/min), any time	11 (25)	10 (48)	7 (28)	0.170
Mean arterial pressure < 60 mmHg, any time	22 (50)	7 (33)	10 (40)	0.414
Vasoactive injections				
Received medication, during recruitment maneuvers	—	10 (48)	23 (92)	0.003
Received medication, any time	39 (89)	18 (86)	20 (80)	0.585
Amount, without recruitment maneuver, bolus equivalents	12.0 [15.5]	3.5 [5.3]	10 [13.8]	0.017
Norepinephrine infusion				
Received medication	14 (32)	8 (38)	7 (28)	0.764
Maximal rate, ng · kg^{-1} · min^{-1}	48 ± 34	30 ± 27	40 ± 16	0.174
Cumulative dose, mg/kg	4.5 [8.2]	3.2 [6.0]	5.2 [4.4]	0.403
Duration of infusion, min	143 [64]	147 [42]	177 [37]	0.281
After operation (first postoperative day until hospital discharge)				
Pulmonary complications	2 (5)	1 (5)	2 (8)	0.842

Entries are the mean ± SD, median [interquartile range], or No. (%), where means for vasoactive medication refer only to those who received it. Bolus equivalents are measured in units of single ampoules of 1 + 20 mg for theodrenaline + cafedrine or 5 µg of norepinephrine. The pulmonary complications are explained in the main text. Fluid infusion was entirely crystalloid; no colloids were used. A recruitment maneuver was not performed in the fixed PEEP of 4 to 5 cm H_2O arm. Individualized PEEP indicates designation for the intervention arm, where an individualized PEEP was used; fixed PEEP of 4 to 5 cm H_2O indicates the arm for which a standard PEEP of 4 or 5 cm H_2O was used; fixed PEEP of 12 cm H_2O indicates the arm for which a standard PEEP of 12 cm H_2O was used.

PEEP, positive end-expiratory pressure.

and C).[3] Measures to prevent lung collapse such as avoiding ventilation with 100% oxygen before tracheal extubation or the use of continuous positive airway pressure in the early postoperative phase are therefore needed and are currently under investigation (ADIPO-CPAP, German Clinical Trials Register No. DRKS00013984). If these measures help prevent postoperative lung collapse and preserve the effects of an individualized PEEP strategy compared to a standard PEEP, it is quite plausible that postoperative pulmonary complications can indeed be reduced by mechanical ventilation strategies in obese patients. However, we cannot completely rule out the possibility that those postoperative lung stabilization strategies would be beneficial also in patients who were ventilated intraoperatively with low PEEP, rendering again the use of individualized intraoperative PEEP not superior to low PEEP. Furthermore, the potential gains of individualized PEEP have to be weighed against hemodynamic depression and increased use of vasoactive medication.

Limitations

Analyses combining data from different studies spanning several years may contain systematic bias that is difficult to detect. In our case, there were slight differences in the prescribed tidal volumes and the recruitment maneuvers. However, the patients included in this analysis were all from a single center, had the same inclusion criteria, and were treated by the same team of physicians within 6 yr.

The choice of oxygenation as primary endpoint may not be convincing to all readers. It is important to keep in mind that here we are in the context of predefined low V_Ts and that the analysis of compliance, driving pressure, and ventilation index provide important information on distention in nondependent lung areas.

For practical reasons, PEEP titration was performed in a 30-degree reverse Trendelenburg position, but before initiation of capnoperitoneum. Therefore, individualized PEEP did not take the effects of capnoperitoneum on respiratory system mechanics into account. Furthermore, the capnoperitoneum measurement was done without readjustment of individualized PEEP. However, surgery was performed in the reverse Trendelenburg position in our study, which is supposed to lower pleural pressure counterbalancing the intraabdominal pressure applied during capnoperitoneum. Even if the effect of capnoperitoneum on pulmonary mechanics seems to be limited in obese patients,[41,42] we cannot exclude the possibility that different PEEP values would have been obtained if PEEP titration had been performed after insufflation of capnoperitoneum. Furthermore, our results cannot be fully transferred to other patient populations or to laparoscopic procedures with different patient positioning, even if a recent publication found that comparable individualized PEEP values are necessary in normal-weight patients undergoing laparoscopic surgery in extreme Trendelenburg positioning.[32]

Our study was neither designed nor powered to investigate the impact of an individualized PEEP strategy on the incidence of postoperative pulmonary complications. Considering the slightly higher rate of hemodynamic complications and the time needed for the PEEP titration, we strongly encourage (1) testing whether an individualized PEEP strategy also translates into a lower rate of postoperative pulmonary complications, and (2) searching for alternative methods for individualization of mechanical ventilation that would be more applicable in clinical routine.

Conclusions

In obese patients undergoing laparoscopic surgery, an electrical impedance tomography–based individualized ventilation strategy resulted in variable PEEP that, on average, exceeded the fixed PEEP of 12 cm H_2O used in the PROBESE study. Compared with the strategy that uses PEEP of 12 cm H_2O, individualized PEEP was associated with higher intraoperative respiratory system compliance and better oxygenation and distribution of ventilation to dependent lung areas—all consistent with higher alveolar recruitment. These benefits vanished after extubation. If alveolar recruitment with individualized PEEP can be preserved by applying adequate measures after tracheal extubation, it will be important to determine if this translates to a lower rate of postoperative pulmonary complications.

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Competing Interests

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