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ORIGINAL ARTICLE

Distribution of ventilation and oxygenation in surgical obese patients ventilated with high versus low positive end-expiratory pressure

A substudy of a randomised controlled trial

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BACKGROUND Intra-operative ventilation using low/physiological tidal volume and positive end-expiratory pressure (PEEP) with periodic alveolar recruitment manoeuvres (ARMs) is recommended in obese surgery patients.

OBJECTIVES To investigate the effects of PEEP levels and ARMs on ventilation distribution, oxygenation, haemodynamic parameters and cerebral oximetry.

DESIGN A substudy of a randomised controlled trial.

SETTING Tertiary medical centre in Geneva, Switzerland, between 2015 and 2018.

PATIENTS One hundred and sixty-two patients with a BMI at least 35 kg per square metre undergoing elective open or laparoscopic surgery lasting at least 120 min.

INTERVENTION Patients were randomised to PEEP of 4 cmH$_2$O ($n = 79$) or PEEP of 12 cmH$_2$O with hourly ARMs ($n = 83$).

MAIN OUTCOME MEASURES The primary endpoint was the fraction of ventilation in the dependent lung as measured by electrical impedance tomography. Secondary endpoints were the oxygen saturation index (SaO$_2$/FIO$_2$ ratio), respiratory and haemodynamic parameters, and cerebral tissue oximetry.

RESULTS Compared with low PEEP, high PEEP was associated with smaller intra-operative decreases in dependent lung ventilation [-11.2%; 95% confidence interval (CI) -8.7 to -13.7 vs. -13.9%; 95% CI -11.7 to -16.5; $P = 0.029$], oxygen saturation index (-49.6%; 95% CI -48.0 to -51.3 vs. -51.3%; 95% CI -49.6 to -53.1; $P < 0.001$) and a lower driving pressure (-6.3 cmH$_2$O; 95% CI -5.7 to -7.0). Haemodynamic parameters did not differ between the groups, except at the end of ARMs when arterial pressure and cardiac index decreased on average by -13.7 mmHg (95% CI -12.5 to -14.9) and by -0.54 l min^{-1} m^{-2} (95% CI -0.49 to -0.59) along with increased cerebral tissue oximetry (3.0 and 3.2% on left and right front brain, respectively).

CONCLUSION In obese patients undergoing abdominal surgery, intra-operative PEEP of 12 cmH$_2$O with periodic ARMs, compared with intra-operative PEEP of 4 cmH$_2$O without ARMs, slightly redistributed ventilation to dependent lung zones with minor improvements in peripheral and cerebral oxygenation.

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KEY POINTS

- In obese patients, small airway and alveolar collapse tends to develop during anaesthesia and mechanical ventilation.
- Although the use of low/physiological tidal volume with PEEP and ARM has been largely advocated to prevent lung injury and atelectasis, the level of PEEP and the impact of ARM on respiratory, haemodynamic and oxygenation parameters remain controversial.
- Compared with a PEEP level of $4\,cmH_2O$, setting the PEEP at $12\,cmH_2O$ with hourly ARMs resulted in a small gain in dependent lung ventilation along with lower driving pressure and minor improvements in systemic oxygenation.
- At the end of each ARM, cerebral tissue oxygenation increased, whereas cardiac index and blood pressure transiently decreased.

Introduction

Up to 28% of European and 38% of American citizens are obese.[1] Following major surgery, obesity is associated with prolonged hospital stay due to poor wound healing, surgical site infection, sepsis and myocardial infarction, as well as pulmonary complications.[2,3] After anaesthesia induction in supine position, lung volume and oxygenation capacity are reduced, and these changes are amplified in morbidly obese patients.[4] The reduced chest wall compliance results in a restrictive syndrome with heterogeneous distribution of the tidal volume (V_T) that worsens during laparoscopic or robotic surgery due to abdominal gas insufflation.[5] As peripheral airway closure occurs within a tidal breath, atelectasis and cyclic alveolar collapse tend to develop in the most dependent lung areas.

Application of positive end-expiratory pressure (PEEP) with periodic alveolar recruitment manoeuvres (ARMs) has been shown to be effective in preventing and reversing atelectasis formation and cyclic alveolar collapse.[6–9] Thoracic electrical impedance tomography (EIT), cardiac output monitor using pulse contour analysis and near-infrared spectroscopy (NIRS) have emerged as effective and reliable tools to assess the distribution of ventilation through the lungs as well as systemic and regional oxygen delivery in anaesthetised mechanically ventilated patients.[10]

In a multicentre randomised clinical trial in adult obese patients undergoing elective abdominal surgery, the 'PROBESE' study, intra-operative ventilation with PEEP at $12\,cmH_2O$ combined with periodic ARMs was not effective in reducing postoperative pulmonary complications (PPCs) compared with a lower PEEP ($4\,cmH_2O$) without ARMs.[11] It remains uncertain whether a ventilation strategy that uses higher PEEP and ARMs improves the distribution of V_T without compromising cardiac output and cerebral oxygen delivery. Given the association between intra-operative cerebral oxygen desaturation and postoperative delirium, the effects of different ventilatory strategies on brain oxygenation needs to be examined.[12,13] In the current substudy, therefore, we investigated the effects of the two ventilatory strategies on the distribution of ventilation in the dependent lungs, respiratory mechanics and haemodynamic parameters, as well as peripheral and cerebral oxygenation.

Materials and methods

Ethics

This substudy of the PROBESE multicentre trial was conducted from January 2015 to May 2018 at the University Hospital of Geneva, Switzerland. The protocols of the parent clinical trial, and this local prospective study were approved on 12 January 2015 by the Ethics Commission for Research of the Canton of Geneva (Chairperson Prof. Bernard Hirschel, rue Gabrielle-Perret Gentil 4, CH-1211 Genève) under the number CCER 14–238. All patients were informed about the research purposes along with the practical aspects and gave written informed consent prior to inclusion.

Patients

Selection criteria for this trial included a BMI at least $35\,kg$ per square metre, elective open or laparoscopic surgery lasting at least $120\,min$ and an intermediate to high risk of PPCs as indicated by the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score at least 26.[14] Patients with previous lung surgery, chemotherapy or radiotherapy (within last 60 days) or mechanical ventilation (within last 30 days) were excluded.

Protocol and group allocation

After arrival in the operating room, nonpremedicated patients were connected to a multiparameter haemodynamic monitor (Philips IntelliVue X2, Amsterdam, the Netherlands) to measure mean arterial pressure (MAP), heart rate (HR) and arterial oxygen saturation (SaO_2). Continuous non-invasive arterial pulse wave analysis using finger cuff technology allowed determination of stroke volume (SV; CNAP Monitor 500; CN Systems Medizintechnik AG, Graz, Austria), whereas near-infrared oximetry (Foresight device; CAS Medical Systems Inc., Branford, Connecticut, USA) allowed monitoring of cerebral tissue oxygenation ($SctO_2$) in left and right frontal brain areas. To assess regional ventilation, a 16 electrode silicone belt of appropriate size to match chest circumference was placed at the level of the fourth or fifth intercostal space with a reference electrode on the anterior midline and connected to the EIT monitor (Pulmovista 500; Dräger Medical GmbH, Lübeck, Germany).

Balanced anaesthesia was administered using desflurane or sevoflurane, low-dose opiates and muscle relaxants targeting bispectral index values between 40 and 60. Intravenous crystalloids and vasopressors were given to support blood pressure. Following orotracheal intubation, volume-controlled ventilation (Aisys CS2; GE Healthcare, Fairfield, Connecticut, USA) was provided with a V_T of 7 ml kg^{-1} predicted body weight (PBW), respiratory rate at 12 min^{-1} and inspiratory oxygen fraction (FIO$_2$) set to 0.4 and adjusted to keep SaO$_2$ at least 92%. The inspiratory to expiratory (I:E) ratio, inspiratory time and respiratory rate were adjusted to maintain end-tidal carbon dioxide partial pressure between 35 and 45 mmHg. Patients were randomly assigned to receive either a PEEP of 4 cmH$_2$O (low PEEP group) or a PEEP of 12 cmH$_2$O with ARMs started after endotracheal intubation and repeated hourly (high PEEP group). The randomisation process has been published elsewhere.[11,15] The ARMs were achieved by stepwise increase of V_T (+4 ml kg^{-1} of PBW) up to plateau pressure of 40 to 50 cmH$_2$O. All patients were planned to be extubated in the operating room at the end of surgery after reversal of neuromuscular blockade.

Measurements

Respiratory mechanical parameters were recorded from the ventilator display screen, including V_T, PEEP, RR, SpO$_2$, FIO$_2$, end-tidal carbon dioxide fraction (FetCO$_2$), peak inspiratory pressure and plateau pressure (P$_{Plateau}$). Standard formulas were used to calculate the driving pressure ($\Delta P = P_{Plateau}$ - PEEP), dynamic compliance (C$_{Dyn} = V_T/\Delta P$), cardiac index (CI = SV × HR/body surface area) and a pulmonary oxygenation index (SaO$_2$/FIO$_2$).[16] Average tidal EIT-images were constructed from voltage profiles generated by cyclic injections of rotating electrical currents,[17] and the impedance tidal variation (ITV) was calculated as the difference between the end-expiratory and the end-inspiratory relative impedance. Tidal EIT-images were subdivided into four horizontal regions of interest (from top to bottom: ROI I, II, III and IV) and numerical values indicated the percentage of total ventilation in each layer within 15 s time periods. Tidal EIT-images in ROI-III and ROI-IV reflected ventilation of the dependent lung region (VDL) and EIT-images in ROI-I and ROI-II reflected regional ventilation of the nondependent lung. Before anaesthesia induction, patients were prompted to breathe steadily for 3 min at a regular pace (12 to 16 cycles per minute), and over the last minute of spontaneous respiration, all EIT measurements were obtained. Intra-operatively, EIT measurements were taken when the electrocautery was not used.

All respiratory and haemodynamic parameters were recorded at four (respiratory mechanics, FetCO$_2$) or five (oxygenation index and EIT) time points (supplemental Figure 1, http://links.lww.com/EJA/A760): before anaesthesia induction (awake), 5 min after induction and intubation (postinduction) and 1, 2 and 3 h after intubation or at the end of surgery (H1, H2 and H3, respectively). In the high-PEEP group, additional respiratory and haemodynamic measurements were done at the end of each ARM.

Endpoints

The primary endpoint was the fraction of VDL as measured by EIT; secondary endpoints included the SaO$_2$/FIO$_2$ ratio, respiratory and haemodynamic parameters as well as SctO$_2$.

Statistical analysis

The sample size calculation indicated that 72 patients per group were required to detect a relative increase of 10% in VDL in the high PEEP group, given the observed VDL values in the low PEEP group and the corresponding covariance matrix of the cohort (assuming an $\alpha = 0.05$ and a power of 80%). Continuous variables were reported as means with standard deviations (SD) or 95% confidence interval (CI) or median with interquartile range [IQR], and categorical variables as frequencies (%). Continuous variables were compared using a Student's t-test or Wilcoxon rank-sum test and categorical variables using χ^2 test or Fisher exact test. Standardised differences (STDs) were used to assess imbalances between baseline characteristics between the two groups. Repeated-measures mixed models were used to estimate the between and within-individual effects of high PEEP on ventilatory and haemodynamic parameters. Pairwise comparisons with Sidak-Bonferroni correction were carried out to analyse the treatment effect at each time point. The effect of ARMs on haemodynamic and ventilatory parameters in the high PEEP group was estimated using repeated-measures mixed models and paired t-tests. All analyses were performed using STATA 17 software (Stata Corp, College Station, Texas, USA).

Results
Study population

A total of 249 patients were enrolled and measurements of EIT, haemodynamic, respiratory and oximetric parameters were obtained in 162 patients who were included in this substudy (Fig. 1). Patient characteristics and intra-operative procedural features did not differ between the two groups (Table 1). As in the parent study, the incidence of PPCs, the need for respiratory therapy and the hospital length of stay did not differ between the two groups (supplemental Table 1, http://links.lww.com/EJA/A760). The intra-operative volume of crystalloids infused and the need for vasopressors was similar in the two groups (supplemental Table 2, http://links.lww.com/EJA/A760).

Primary endpoint

Pre-operatively, VDL under spontaneous ventilation in supine position did not differ between the two groups (49.3%; 95% CI 48.0 to 50.7 vs. 50.5%; 95% CI 49.4 to 51.7

Fig. 1 CONSORT flow diagram.
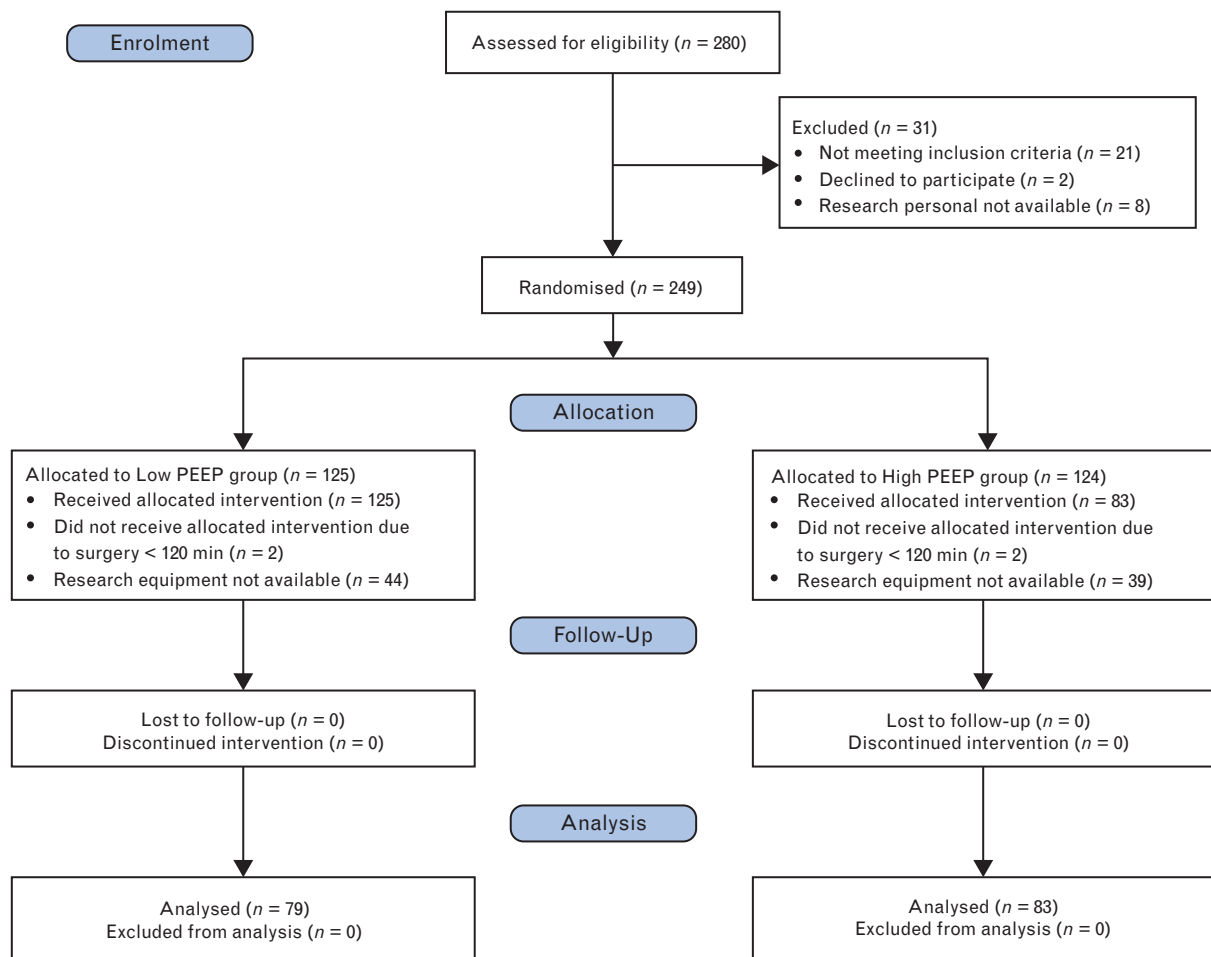
in high-PEEP and low-PEEP groups, respectively). Following anaesthesia induction and initiation of mechanical ventilation, the reduction in VDL was smaller in the high PEEP than in the low PEEP group (-11.2%; 95% CI -8.7 to -13.7 vs. -13.9%; 95% CI -11.7 to -16.5 resulting in higher VDL (+2.7%; 95% CI 1.3 to 4.1, Fig. 2). At the end of periodic ARMs, VDL increased on average by 5.4% (95% CI 4.3 to 6.5) without reaching baseline values. After head-up positioning and gas insufflation in the abdomen, there were no changes in the distribution of V_T and VDL remained stable till the end of surgery. The distribution of tidal EIT in the four ROI is illustrated in supplemental Figures 2 and 3, http://links.lww.com/EJA/A760.

Secondary endpoints and posthoc analysis
Compared with baseline, SaO_2/FIO_2 decreased in both groups after starting mechanical ventilation (-49.6%; 95% CI -48.0 to -51.3 and -51.3%; 95% CI -49.6 to -53.1 in the high and low PEEP group, respectively) but remained slightly higher in the high PEEP group compared with

the low PEEP group (+2.7%; 95% CI 1.3 to 4.1) (Fig. 3). At the end of each periodic ARM, there was a small increase in SaO_2/FIO_2.

As summarised in Table 2, the high PEEP group exhibited higher mean $P_{Plateau}$ than the low PEEP group with lower ΔP and higher C_{Dyn}. After 180 min of mechanical ventilation, C_{Dyn} decreased in the low PEEP group, whereas it remained unchanged in the high PEEP group. There was no correlation between intra-operative measurements of ΔP and VDL in the two groups ($R^2 = 0.0002$ and 0.0074 in the low and high PEEP group, respectively) (supplemental Figure 4, http://links.lww.com/EJA/A760). Likewise, transient gains in VDL following ARMs (<10%, 10 to 25% or > 25%) were not associated with significant reductions in ΔP (supplemental Figure 5, http://links.lww.com/EJA/A760).

Intra-operatively, haemodynamic parameters did not differ between the two groups (Fig. 4). ARMs transiently decreased MAP (-13.7 mmHg; 95% CI -12.5 to -14.9) and CI (-0.54 l min^{-1} m^{-2}; 95% CI -0.49 to -0.59).

Table 1 Pre-operative patient characteristics and intra-operative surgical data

Variable	Low PEEP ($n = 79$)	High PEEP ($n = 83$)	STD
Demographics			
Age, years	45.4 ± 10.6	45.5 ± 11.4	-0.01134
Male, %	20 (25.3)	25 (30.1)	0.10748
BMI, kg m^{-2}	43.5 ± 6.9	44.4 ± 8.0	-0.11999
Scores			
ARISCAT Score	43.6 ± 5.9	43.0 ± 6.5	0.10771
Waist-to-hip ratio	1.03 ± 0.10	1.02 ± 0.08	0.14444
ASA-PS classes III and IV	26 (32.9)	30 (36.1)	0.06804
Comorbidities, %			
Hypertension	68 (86.1)	72 (86.7)	0.01958
Obstructive sleep apnoea	42 (53.2)	49 (59.0)	0.11852
Chronic obstructive pulmonary disease	1 (1.3)	4 (4.8)	0.20801
Use of non-invasive ventilatory support	28 (35.4)	32 (38.6)	0.06447
Diabetes mellitus	18 (22.8)	21 (25.3)	0.05891
Gastroesophageal reflux	69 (87.3)	72 (86.7)	0.01771
Alcohol intake > 20 g day^{-1}	9 (11.4)	10 (12.0)	0.02039
Pre-operative laboratory tests			
Haemoglobin, g dl^{-1}	13.7 ± 1.4	13.5 ± 1.5	0.16404
Creatinine, mcm dl^{-1}	68 [60 to 82]	65 [57 to 75]	-0.26057
Type of anaesthesia, %			
Balanced general anaesthesia	77 (97.5)	82 (98.8)	0.09811
Thoracic epidural analgesia	2 (2.5)	1 (1.2)	0.09811
Patient position			
Head up	74 (93.7)	74 (89.2)	0.16166
Head down	1 (1.3)	4 (4.8)	0.20801
Supine position	4 (5.1)	5 (6.0)	0.04200
Surgical approach, %			
Open surgery	4 (5.1)	0 (0.0)	0.32660
Laparoscopic surgery	45 (57.0)	50 (60.2)	0.06661
Robotic surgery	30 (38.0)	33 (39.8)	0.03661
Intra-abdominal pressure, mmHg[a]	14.7 ± 1.0	14.8 ± 0.7	-0.11704
Temperature at end of surgery, °C	36.9 ± 0.2	36.8 ± 0.2	0.05587
Duration of anaesthesia, min	309.5 ± 56.6	327.5 ± 78.1	-0.26442
Duration of surgery, min	229.6 ± 57.7	239.7 ± 72.3	-0.15300

Data are presented as mean $\pm$ standard deviation, number (percentage) or median [interquartile range]. ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA-PS, American Society Association Physical status; SpO2, pulse oximetry; STD, standardised difference. [a] If laparoscopic or robotic surgery.

Intra-operatively, SctO$_2$ in the right and left sides remained unchanged in the high PEEP group and small decreases in SctO$_2$ occurred over time in the low PEEP group (Fig. 4). Following ARMs, SctO$_2$ increased slightly (3.0 and 3.2% on left and right front brain, respectively).

Discussion

In this cohort of obese patients undergoing abdominal surgery and at risk of PPCs, a ventilatory strategy using low/physiological V$_T$ and a PEEP of 12 cmH$_2$O with periodic ARMs compared with a PEEP of 4 cmH$_2$O without ARMs resulted in minor redistribution of ventilation in the dependent part of the lungs, with transient further gain during ARMs; higher P$_{Plateau}$ with reduction in ΔP but no correlation between the fall in ΔP and improved VDL; and similar haemodynamics and minor improvements in SctO$_2$, with transient decreases in CI and MAP during ARMs.

In this large sample of obese patients, EIT allowed real-time non-invasive imaging of regional lung aeration and it was used to compare the effects of higher to lower PEEP levels on the distribution of V$_T$ through the lungs. Analysis of tidal impedance variations has been validated in mechanically ventilated patients against spirometry for V$_T$ measurements and computed tomography to detect atelectasis formation, alveolar recruitment and overdistension.[18,19] Placing the EIT belt at the fourth to fifth intercostal space generates a 5 to 10 cm wide cross-section in the thorax and represents a valuable compromise to describe the distribution of V$_T$ through the middle part of the lungs while avoiding interferences due to surgical manipulation.[20] Respiratory mechanics, systemic and cerebral oxygenation variables were collected at different times during surgery as well as before and after ARMs. This made possible to explore the association between the changes in regional lung aeration, respiratory mechanical function, and haemodynamic parameters at two levels of PEEP with or without periodic ARMs.

Following anaesthesia induction, mechanical ventilation with physiological V$_T$ resulted in a moderate shift of ventilation from dependent to nondependent lung areas with reduction in pulmonary oxygen uptake reflecting

Fig. 2 Effect of intra-operative high positive end-expiratory pressure with recruitment manoeuvres vs. low PEEP on ventilation of the dependent lung part in obese patients.

Treatment effect, $P = 0.029$; Recruitment effect, $P < 0.001$; Interaction, $P = 0.335$
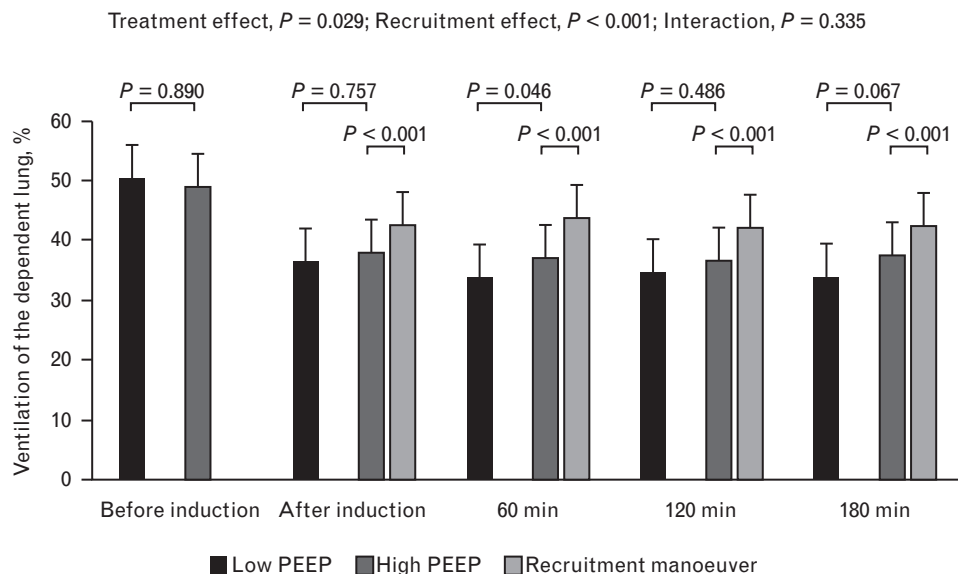
greater ventilation-perfusion mismatch, as previously reported in cardiac and visceral surgery.[5,21,22] In our patients, pre-operative oxygenation with FIO_2 of 1.0 promoted absorption atelectasis in the dependent well perfused lung parts, whereas the reverse Trendelenburg position favoured caudal displacement of the diaphragm, along with some preservation of lung volumes in the dorso-caudal pulmonary regions.[23] Compared with low PEEP at $4 \, cmH_2O$, moderate PEEP at $12 \, cmH_2O$ coupled with periodic ARMs resulted in slightly higher $P_{Plateau}$ ($+1.7 \, cmH_2O$) with a marginal gain in dorsal ventilation ($+2.7\%$) and lesser stress on lung structures as

Fig. 3 Effect of intra-operative high positive end-expiratory pressure with recruitment manoeuvres vs. low PEEP on the ratio of pulsed-oxygen saturation (SaO_2)/fractional inspired oxygen (FiO_2) in obese patients.

Treatment effect, $P < 0.001$; Recruitment effect, $P < 0.001$; Interaction, $P = 0.039$
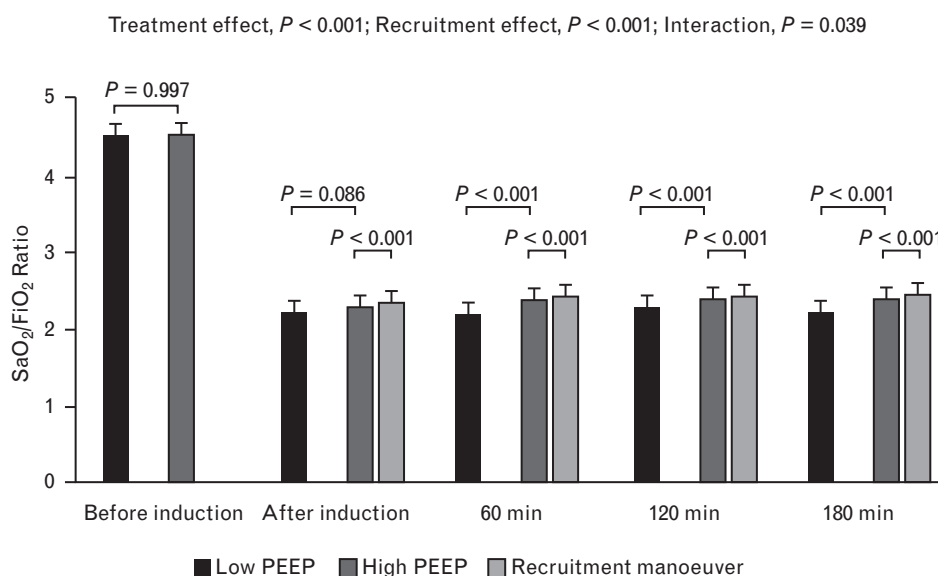
Table 2 Effect of high positive end-expiratory pressure with recruitment manoeuvres vs. low positive end-expiratory pressure on respiratory parameters in obese patients

Variable	Low PEEP (n = 79)	High PEEP (n = 83)	High PEEP End recruitment	P [a]
Tidal volume ml kg^{-1} PBW^{-1}				
Post induction	7.2 ± 0.9	7.3 ± 0.8	14.2 ± 2.4	0.824
60 min	7.2 ± 0.9	7.3 ± 0.8	14.5 ± 2.4	0.616
120 min	7.2 ± 0.9	7.2 ± 0.8	14.3 ± 2.5	0.840
180 min	7.3 ± 0.9	7.4 ± 0.9	13.9 ± 3.0	0.462
Plateau pressure, cmH$_2$O				
Post induction	24.2 ± 4.4	26.1 ± 4.0	35.0 ± 4.1	0.004
60 min	24.4 ± 4.2	26.1 ± 4.2	35.4 ± 3.8	0.012
120 min	25.1 ± 4.1	26.4 ± 4.0	35.5 ± 5.0	0.038
180 min	25.0 ± 4.3	26.7 ± 3.8	35.4 ± 4.7	0.008
Fractional inspiratory oxygen concentration, %				
Post induction	0.45 ± 0.06	0.44 ± 0.05	0.44 ± 0.05	0.215
60 min	0.45 ± 0.06	0.41 ± 0.02	0.41 ± 0.02	0.001
120 min	0.45 ± 0.06	0.41 ± 0.02	0.41 ± 0.02	<0.001
180 min	0.45 ± 0.06	0.41 ± 0.01	0.41 ± 0.01	<0.001
End-tidal carbon dioxide fraction, %				
Postinduction	5.4 ± 0.4	5.4 ± 0.4	5.0 ± 0.2	0.825
60 min	5.5 ± 0.4	5.5 ± 0.4	5.0 ± 0.3	0.945
120 min	5.6 ± 0.4	5.5 ± 0.5	4.9 ± 0.3	0.876
180 min	5.7 ± 0.3	5.6 ± 0.4	5.0 ± 0.3	0.892
Driving pressure, cmH$_2$O				
Post induction	20.2 ± 4.4	14.1 ± 4.0	23.0 ± 4.1	< 0.001
60 min	20.4 ± 4.2	14.1 ± 4.2	23.4 ± 3.8	< 0.001
120 min	21.1 ± 4.1	14.5 ± 4.2	23.5 ± 5.0	< 0.001
180 min	21.0 ± 4.3	14.7 ± 3.8	23.4 ± 4.7	< 0.001
Compliance, ml cmH$_2$O^{-1}				
Post induction	26.4 ± 7.0	31.6 ± 9.1	38.9 ± 10.6	< 0.001
60 min	25.6 ± 5.5	32.5 ± 11.2	39.0 ± 10.2	< 0.001
120 min	24.2 ± 4.5	30.8 ± 8.4	39.2 ± 10.0	< 0.001
180 min	22.8 ± 4.2	30.2 ± 7.5	39.8 ± 9.9	< 0.001

Data are presented as mean ± standard deviation. PBW, predicted body weight. [a] High PEEP vs. low PEEP.

reflected by lower driving pressure (-6.3 cmH$_2$O) and higher C$_{Dyn}$ (+ 6.6 ml cmH$_2$O^{-1}). In both obese and nonobese anesthetised patients, combining a PEEP at 8 to 10 cmH$_2$O with periodic ARMs has been shown to be effective in increasing respiratory compliance, oxygenation and lung aeration in contrast with PEEP at 0 to 2 cmH$_2$O and no ARMs.[21,22,24–26] In our cohort, we found no correlation between the changes in ΔP and VDL in both groups. Moreover, the small improvements in dorsal lung aeration and systemic oxygenation were only transient and failed to reach pre-operative levels following each ARM. In similar obese surgical patients, it has been demonstrated that repeating ARM every 10 min in addition to setting a PEEP level at 10 cmH$_2$O was necessary to provide consistent improvement in respiratory compliance and oxygenation.[27] Altogether, lung imaging and physiological data suggest that setting a PEEP at 10 to 12 cmH$_2$O with hourly ARM does not consistently reverse respiratory disturbances induced by anaesthesia and mechanical ventilation and that ΔP derived from ventilator circuit measurements (P$_{Plateau}$ - PEEP) is a poor indicator of optimal lung recruitment in obese individuals with uninjured lungs. Considering the interference of respiratory mechanical properties with patients' characteristics (e.g. BMI, fat distribution, thoraco-abdominal anatomy), positioning and

surgical approach (e.g. pneumoperitoneum, laparotomy), optimising the PEEP levels in each individual has been advocated by targeting the best compliance (PEEP titration trial) or an end-expiratory transpulmonary pressure of 0 cmH$_2$O (oesophageal pressure) or by minimising lung collapse and overdistension (EIT lung imaging).[6,8,28,29] Application of such open-lung ventilation strategy requires higher PEEP levels ($\sim$15 to 23 cmH$_2$O) than in our study and has been shown effective at lowering mechanical stress, increasing oxygenation and end-expiratory lung volume with more homogeneous V$_T$ distribution as evidenced by lesser collapsed and distended lung areas in obese patients during abdominal surgery.[6,8,29,30] However, the intra-operative respiratory benefits of higher PEEP levels with periodic ARMs disappear shortly after anaesthesia emergence and do not translate into better clinical respiratory outcomes.[8,22,31] Although current evidence suggests that the use of low/physiological tidal volume or physiological V$_T$ improves clinical outcomes,[32] the role of ΔP for titrating ventilation and the optimal settings of PEEP with periodic ARMs in obese patients remain unclear and deserve further investigation.

In this study, haemodynamic parameters and cerebral oxygenation were similarly preserved at higher and lower PEEP. During ARMs, hyperventilation and limitation in venous return due to larger tidal volumes with higher intrathoracic pressure produced transient reduction in FetCO$_2$, CI and MAP. The acute hypocapnic cerebral vasoconstriction resulting from the observed mean 0.5% reduction in FetCO$_2$ ($\sim$ -4 mmHg arterial CO$_2$ pressure) was expected to lower cerebral blood flow by 8 to 12% and would be reflected by a 3 to 4% fall in SctO$_2$ in normoxic conditions.[33,34] In contrast, we observed an average 3% increase in SctO$_2$ following ARMs, suggesting that the improved blood oxygenation (SaO$_2$/FIO$_2$) consequent to increased dorsal lung aeration overcompensated the hypocapnic vasoconstriction within the cerebral autoregulatory range (e.g. MAP maintained above 70 mmHg). These favourable findings differ from those reported in patients undergoing carotid endarterectomy and in mechanically ventilated patients with brain injury or acute respiratory distress syndrome, in whom ARMs are often associated with impaired systemic haemodynamic and worsened cerebral oxygenation with no improved systemic oxygenation.[35–37] In summary, these results suggest that ARMs may transiently increase cerebral oxygenation in normovolaemic patients with preserved cerebrovascular autoregulation and no elevated intracranial pressure.[38] Optimising oxygen delivery to the brain is clinically relevant, as avoidance of cerebral oxygen desaturation has been associated with less postoperative cognitive dysfunction.[39]

This study has limitations. Firstly, as designed in the original PROBESE study, we compared the effects of two levels of PEEP that were lower than those reported in individualised PEEP trials wherein larger improvements in dependent lung aeration with higher respiratory

Fig. 4 Intra-operative effects of high positive end-expiratory pressure (PEEP) with recruitment manoeuvres *vs.* low PEEP on mean arterial blood pressure, cardiac output as well as left and right-sided cerebral near-infrared spectroscopy (NIRS).
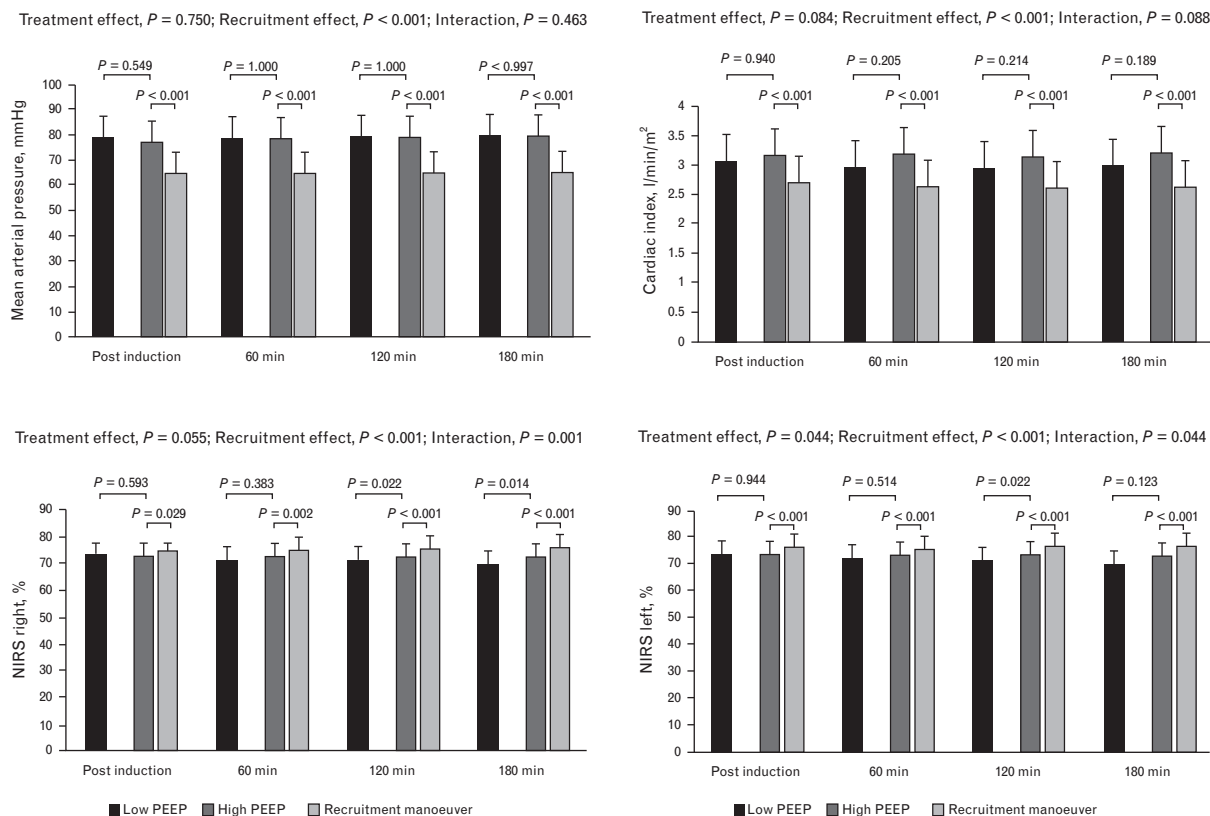
compliance were reported in anaesthetised obese patients.[6–8,27,28] Secondly, different protocols of ARMs using continuous positive pressure over 30 to 60 s or stepwise increase in V_T or PEEP levels could yield different haemodynamic and respiratory effects.[40] Thirdly, our results obtained this single-centre substudy with obese patients undergoing laparoscopic surgery lasting on average 4 h in reverse Trendelenburg position could not be extrapolated in other type of surgery and in patients with diseased/injured lungs. Although higher (compared with lower) levels of PEEP are associated with physiological improvements and clinical benefits in critically ill patients with or without acute respiratory distress syndrome, the impact of obesity in adjusting well tolerated levels of PEEP has not been explored so far.[41,42] Given the worldwide obesity epidemic, further well designed and powered studies are needed to examine the optimal ventilatory strategy in the increasing numbers of obese patients who may require emergency surgery following trauma or sepsis.

In conclusion, in obese anaesthetised patients undergoing abdominal surgery in reverse Trendelenburg position, intra-operative application of a PEEP at 12 cmH$_2$O with periodic ARMs compared with a PEEP at 4 cmH$_2$O without ARMs, slightly redistributed ventilation to dependent lung areas along with minor improvements in respiratory mechanics as well as peripheral and cerebral oxygenation.

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