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ORIGINAL RESEARCH

Physiological effects of two driving pressure-based methods to set positive end-expiratory pressure during one lung ventilation

Savino Spadaro[1] · Salvatore Grasso[2] · Dan Stieper Karbing[3] · Giuseppe Santoro[1] · Giorgio Cavallesco[4] · Pio Maniscalco[4] · Francesca Murgolo[2] · Rosa Di Mussi[2] · Riccardo Ragazzi[1] · Stephen Edward Rees[3] · Carlo Alberto Volta[1] · Alberto Fogagnolo[1]

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Abstract

During one-lung ventilation (OLV), titrating the positive end-expiratory pressure (PEEP) to target a low driving pressure (ΔP) could reduce postoperative pulmonary complications. However, it is unclear how to conduct PEEP titration: by stepwise increase starting from zero PEEP ($PEEP_{INCREMENTAL}$) or by stepwise decrease after a lung recruiting manoeuvre ($PEEP_{DECREMENTAL}$). In this randomized trial, we compared the physiological effects of these two PEEP titration strategies on respiratory mechanics, ventilation/perfusion mismatch and gas exchange. Patients undergoing video-assisted thoracoscopic surgery in OLV were randomly assigned to a $PEEP_{INCREMENTAL}$ or $PEEP_{DECREMENTAL}$ strategy to match the lowest ΔP. In the $PEEP_{INCREMENTAL}$ group, PEEP was stepwise titrated from ZEEP up to 16 cm H_2O, whereas in the $PEEP_{DECREMENTAL}$ group PEEP was decrementally titrated, starting from 16 cm H_2O, immediately after a lung recruiting manoeuvre. Respiratory mechanics, ventilation/perfusion mismatch and blood gas analyses were recorded at baseline, after PEEP titration and at the end of surgery. Sixty patients were included in the study. After PEEP titration, shunt decreased similarly in both groups, from 50 [39–55]% to 35 [28–42]% in the $PEEP_{INCREMENTAL}$ and from 45 [37–58]% to 33 [25–45]% in the $PEEP_{DECREMENTAL}$ group (both $p < 0.001$ vs baseline). The resulting ΔP, however, was lower in the $PEEP_{DECREMENTAL}$ than in the $PEEP_{INCREMENTAL}$ group (8 [7–11] vs 10 [9–11] cm H_2O; $p = 0.03$). In the $PEEP_{DECREMENTAL}$ group the PaO_2/ FIO_2 ratio increased significantly after intervention (from 140 [99–176] to 186 [152–243], $p < 0.001$). Both the $PEEP_{INCREMENTAL}$ and the $PEEP_{DECREMENTAL}$ strategies were able to decrease intraoperative shunt, but only $PEEP_{DECREMENTAL}$ improved oxygenation and lowered intraoperative ΔP.

Clinical trial number NCT03635281; August 2018; “retrospectively registered”

Keywords Positive end-expiratory pressure · One-lung ventilation · Shunt · Driving pressure · Oxygenation

1 Introduction

During thoracic surgery with one lung ventilation (OLV), application of positive end-expiratory pressure (PEEP) improves gas exchange and lung mechanics [1–6]. However, the approach to PEEP titration remains controversial.

Spadaro Savino and Grasso Salvatore have contributed equally to this work.

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✉ Savino Spadaro
savinospadaro@gmail.com

1 Department of Morphology, Experimental Medicine and Surgery, Section of Anaesthesia and Intensive Care, Azienda Ospedaliera-Universitaria Sant’ Anna, University of Ferrara, Via Aldo Moro, 8, 44124 Ferrara, Italy

2 Department of Emergency and Organ Transplant (DETO), “Aldo Moro” University of Bari, Bari, Italy

3 Respiratory and Critical Care Group, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

4 Department of Morphology, Experimental Medicine and Surgery, Thoracic Surgery, Azienda Ospedaliera-Universitaria Sant’ Anna, University of Ferrara, Ferrara, Italy

Recently, we documented the highly variable impact of different PEEP levels on alveolar recruitment and gas exchange [2]; our results confirmed the expert's opinions which suggest to personalize PEEP level to balance alveolar recruitment and hyperinflation [3]. Recently, PEEP titration to the "lowest" driving pressure (ΔP), i.e. the difference between inspiratory plateau pressure and total PEEP, has gained a central role in the scientific debate [3–6]. Park et al. found a lower rate of postoperative pulmonary complications (PPC) in patients submitted to an *incremental* PEEP titration to the lowest ΔP [4]. Conversely, other studies suggest an open lung approach based on a *decremental* PEEP trial subsequent a lung recruitment manoeuvre (LRM) [7–10].

To our knowledge, physiological trials comparing the *incremental* versus the *decremental* ΔP-oriented PEEP titration during OLV are lacking.

In this study, we randomly assigned patients scheduled for video-assisted thoracic surgery in OLV to an *incremental* PEEP ($PEEP_{INCREMENTAL}$) versus an open lung approach with *decremental* PEEP titration ($PEEP_{DECREMENTAL}$). Our hypothesis was that the $PEEP_{DECREMENTAL}$ approach would result in more improvement in the respiratory mechanics, ventilation/perfusion mismatch and gas exchange compared to the $PEEP_{INCREMENTAL}$ technique.

2 Methods

The trial was approved by the Ethics Committee of our institution (protocol N.11072017) and written informed consent was obtained from each patient before surgery. The trial was registered in Clinicaltrial.gov (NCT03635281). The study was performed in the Department of Anaesthesia and Intensive Care at the University Hospital of Ferrara (Italy) from August 2017 to October 2018. Results are reported according to the Consolidated Standards of Reporting Trials (CONSORT) checklist for randomized trials. The CONSORT Checklist is reported in Supplement file 1.

2.1 Population

We screened all patients scheduled for video-assisted thoracoscopic surgery (i.e. lobectomy or wedge resection) requiring lateral position and OLV for at least 2 h. Exclusion criteria were: ASA (American Society of Anesthesiologists Physical Status Classification) score ≥ 4, severe chronic respiratory failure (chronic obstructive pulmonary disease patients with Global Initiative for Chronic Obstructive Lung Disease stage 3 or 4), preoperative haemoglobin less than 10 g dl^{-1}, hemodynamic instability during LRM defined as a decrease in systolic arterial pressure of more than 20% from baseline, and unplanned thoracotomy conversion.

The day before the procedure, all patients underwent spirometry in sitting position according to the American Thoracic Society's standards (SpiroPro; Jaeger, Germany). Spirometry measurements included vital capacity, forced expiratory volume in the 1st second (FEV_1), forced vital capacity (FVC), expiratory reserve volume (ERV), and transfer coefficient (KCO).

2.2 Anesthesia

Anaesthesia was induced with propofol (1.5 to 2 mg kg^{-1}), fentanyl (3 µg kg^{-1}), and rocuronium (0.6 mg kg^{-1}). Target-controlled propofol infusion was performed with estimated effect-site concentration of 2–4 µg ml^{-1}, targeting a bispectral index (Aspect A-2000; Aspect Medical System, USA) of 40–60. Neuromuscular blockade was provided with continuous infusion of rocuronium based on train-of-four neuromuscular monitoring. All patients were breathing 80% oxygen during induction of general anaesthesia. The trachea was intubated with an appropriately sized double lumen tube whose correct positioning was bronchoscopy confirmed. Ultrasound-guided thoracic paravertebral blocks were performed in lateral decubitus with two injections of 8 ml Ropivacaine 0.75% [11]. Appropriate spread of local anaesthetic was confirmed with the movement of the pleura. Patients were ventilated in volume-controlled mode with constant flow using a Dräger Perseus ventilator (Drägerwerk AG and Co. KGaA, Germany). During two-lung (bilateral) ventilation, TV was set to 7 ml kg^{-1} predicted body weight (PBW) and PEEP was set to zero. These settings were maintained for approximately 10 min before shifting to OLV. When OLV started, TV was reduced to 5 ml kg^{-1} (PBW) and PEEP was initially maintained unchanged. PEEP was then adjusted according to the study group (see below). PEEP was applied according to the study group (see below). FiO_2 was set to maintain peripheral oxygen saturation (SpO_2) equal to or greater than 92% while respiratory rate was adjusted to keep arterial $PaCO_2$ between 40 and 60 mmHg.

2.3 Randomization and study intervention

After inclusion in the study, patients were randomized to the $PEEP_{INCREMENTAL}$ or a $PEEP_{DECREMENTAL}$ protocol. Randomization was performed 1:1 using randomization in block sizes of 2 and 4. The time-course of the study is summarized in Fig. 1.

The $PEEP_{INCREMENTAL}$ protocol followed the strategy proposed by Park and coworkers [4]; whereas the $PEEP_{DECREMENTAL}$ protocol followed the strategy proposed by the ongoing "protective ventilation with high versus low positive end-expiratory pressure during one-lung ventilation for thoracic surgery" (PROTHOR) trial [12].

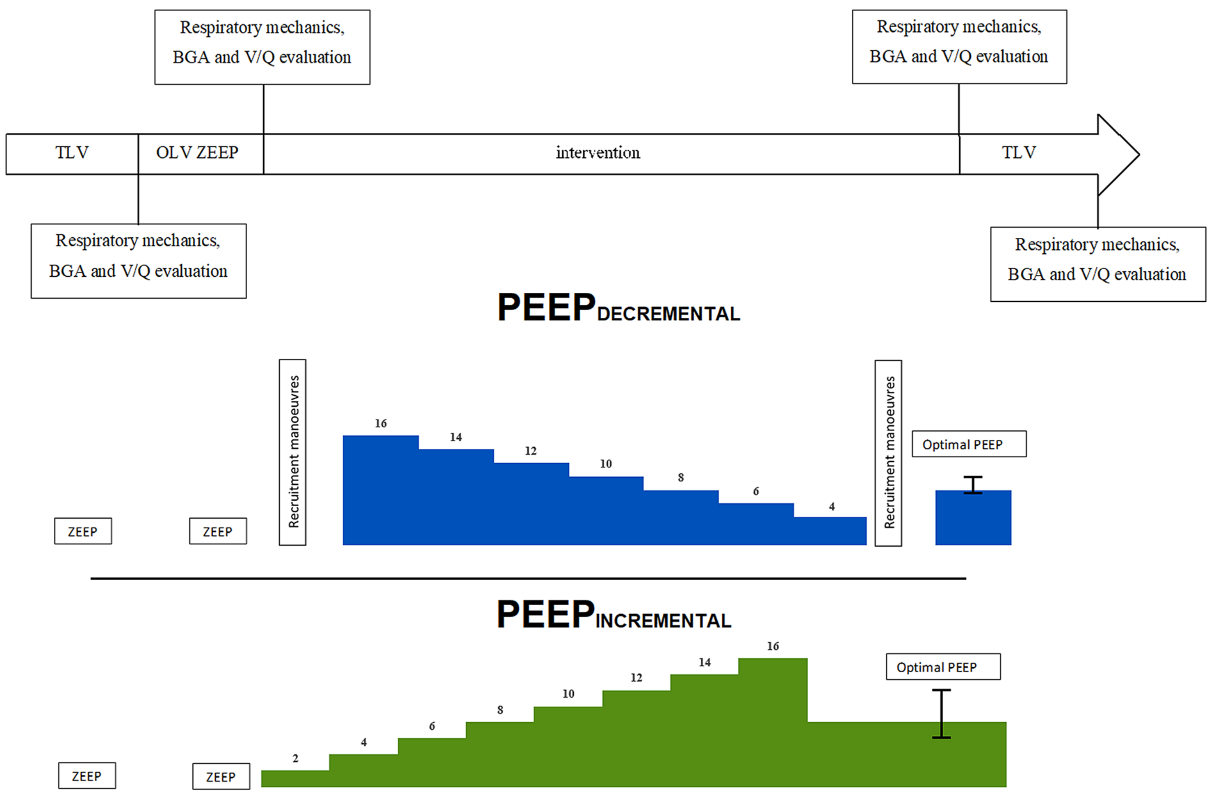

Fig. 1 Resume of study protocol

In the $PEEP_{INCREMENTAL}$ group, PEEP was increased stepwise by 2 cm H_2O steps, from ZEEP up to 16 cm H_2O, while maintaining TV and RR constant. Each PEEP level was kept for 1 min before measuring ΔP. At the end of the PEEP titration trial, the "best" PEEP defined as the level associated with lowest ΔP, was set and maintained until extubation. (see Supplement File 1 for details).

Patients in $PEEP_{DECREMENTAL}$ group were submitted to a LRM immediately followed by a decremental PEEP trial. As part of the LRM, respiratory rate was set to 6 min^{-1} with an inspiratory–expiratory ratio of 1:1. TV was then increased in steps of 2 mL kg^{-1} PBW until reaching a target plateau pressure of 30 cm H_2O. The step increase in TV was performed over a period of 20–30 s. Three breaths were allowed at the target plateau pressure (see Supplement File 2 for details). After performing the LRM, TV and respiratory rate were returned to the starting values, while PEEP was set to 16 cm H_2O. Then PEEP was decreased in steps of 2 cm H_2O, down to 4 cm H_2O, in order to identify the "best" (i.e. the lowest) ΔP. Each level of PEEP was maintained for 1 min before measuring ΔP. Subsequently, another LRM, analogous to the first one, was performed and PEEP was set to the "best" PEEP level identified during the decremental PEEP trial and maintained until extubation. Safety-endpoints for interruption of the LRM were a ± 20% variation in heart rate or a decrease of more than 20% of mean arterial pressure [13].

2.4 Lung mechanics and ventilation/perfusion assessment

Respiratory mechanics were assessed by the constant V′/rapid occlusion method previously described in details [2]. The end-inspiratory plateau pressure was measured as the airway pressure (Paw) at the end of an end-inspiratory occlusion performed by increasing end-inspiratory pause to 40% of the inspiratory time. Driving pressure (ΔP) was calculated as plateau pressure—PEEP; static respiratory system compliance was calculated as TV/(end-inspiratory plateau pressure—PEEP). Mechanical power (J/min) at each time-point was calculated as described by Gattinoni et al. with the following formula [14]:

$$Power = RR * \left\{ \Delta V^2 * \left[\frac{1}{2} * ELrs + RR * \frac{(1 + I:E)}{60 * I:E} * Raw \right] + \Delta V^2 * PEEP \right\}$$

where RR is respiratory rate, ΔV is tidal volume, ELrs is respiratory system elastance and Raw is airway resistance [14, 15].

Total energy load (J) was calculated as the product of power and ventilation time.

Shunt and V/Q matching were assessed by the Beacon Caresystem (Mermaid Care A/S, Denmark) in two-lung ventilation (TLV), OLV before intervention, OLV after intervention and in TLV at the end of the surgery. Briefly, to assess V/Q matching, the automatic lung parameter estimator (ALPE) approach [16, 17] used in the Beacon Caresystem, requires modification of FIO_2 in three or four steps in a process taking 5–10 min. At each FIO_2 level, steady state is identified and measurements are automatically taken of ventilation, SpO_2, O_2 consumption, CO_2 production, and inspiratory and expiratory fractions of O_2 and CO_2. Oxygenation at the various FIO_2 levels are used to estimate shunt and low V/Q mismatch whereas end-tidal to arterial CO_2 gradient is used to calculate high V/Q mismatch. Low V/Q mismatch is reported as the O_2 partial pressure difference between alveolar air and lung capillary blood prior to mixing with shunted venous blood, thus quantifying the primary effect of low V/Q on O_2 exchange. High V/Q mismatch is reported as the CO_2 partial pressure difference between alveolar air and lung capillary blood prior to mixing with shunted venous blood quantifying the primary effect of high V/Q on CO_2 exchange. The ALPE approach has been validated and applied in varied patient populations [1, 18–20] including patients undergoing OLV [2].

2.5 Statistical analysis

All analyses were pre-planned, unless specified as post-hoc. Normal distribution was tested by the Shapiro–Wilk normality test. Data are reported as mean ± SD or median [interquartile range] as appropriate. Differences between measurements were analysed using repeated measures ANOVA or Friedman's rank analysis for data with normal or not normal distribution, respectively. When multiple comparisons were made, p-values were adjusted by the Bonferroni post hoc procedure. Two-tailed statistical hypothesis testing was performed with a p value of ≤ 0.05 considered statistically significant. Statistical analysis was performed using SPSS Statistics for Windows, version 20.0 (IBM, USA).

Several post-hoc analyses were performed. Firstly, we investigated whether the effect of $PEEP_{INCREMENTAL}$ and $PEEP_{DECREMENTAL}$ strategies on the ΔP and PaO_2/FIO_2 could be influenced by baseline ΔP values. To perform this analysis, we divided the population according to a baseline ΔP, either ≤ 14 cm H_2O or > 14 cm H_2O; this cut-off was derived from previous studies performed both in critically ill patients [21] and in one lung ventilation [2]. Furthermore, we investigated whether baseline comorbidities of the patients could influence the response to the two ventilation strategies. With this purpose, we analysed patients stratified for age, body mass index (BMI) or history of COPD.

2.6 Sample size

The sample size was based on the impact of PEEP titration on the shunt fraction (compared to OLV at ZEEP). Based on previous data, we assumed a decrease in shunt of at least 7% in the $PEEP_{DECREMENTAL}$ group [22] and at of least 2% in $PEEP_{INCREMENTAL}$ group [2], with a 6% pooled standard deviation. According to this analysis, including 31 patients in each group was deemed enough to demonstrate a significant difference between the two groups, with an 90% power and a 5% alfa error. Assuming a 5% loss to follow up, for example for unplanned conversion to thoracotomy surgery or intraoperative hemodynamic instability, we planned to enrol 65 patients.

3 Results

3.1 Population

During the study period, 66 patients were screened for eligibility. Of those, 63 met the inclusion criteria and were included in the study; three (3) patients underwent unplanned thoracotomy conversion, leaving 60 patients for final analysis. There were no missing data or protocol deviation during the study. None of the patients analysed were excluded due to intraoperative hemodynamic instability. Preoperative clinical and demographical characteristics of the patients are presented in Table 1. The flowchart of the study is shown in Figure S1.

3.2 V/Q mismatch

After anaesthesia induction, shunt was 25 [19–33] % in TLV and increased to 47 [39–56] % ($p < 0.001$) when patients were posed in lateral decubitus and ventilated in OLV at ZEEP. After PEEP titration, shunt decreased similarly in both groups (Table 2, Fig. 2), from 50 [39–55]% to 35 [28–42]% in the $PEEP_{INCREMENTAL}$ group (mean difference 20 [95% CI 16–25]%; $p < 0.001$ vs baseline) and from 45

Table 1 Characteristic's patients

Variable	All patients n = 60	$PEEP_{INCREMENTAL}$ n = 30	$PEEP_{DECREMENTAL}$ n = 30	p value
Age	68 ± 9	66 ± 8	67 ± 9	0.571
BMI	27.5 ± 5.5	27.0 ± 6.2	27.8 ± 5.5	0.576
ASA score				0.506
II	11	4	7	
III	49	26	23	
Sex (M/F), n	40/20	18/12	22/8	0.411
Surgery side (L/R)	29/31	13/17	15/15	0.312
Type of surgery				0.061
Lobectomy	55	30	25	
Wedge resection	5	–	5	
Duration of MV (min)	212 [175–255]	218 [195–255]	205 [175–255]	0.57
Duration of OLV (min)	192 [166–240]	195 [180–240]	190 [145–240]	0.49
Comorbidities				
Diabetes, n (%)	8 (13)	4 (13)	4 (13)	0.999
Hypertension, n (%)	35 (50)	10 (33)	16 (53)	0.192
Vascular disease, n (%)	20 (33)	10 (33)	10 (33)	0.999
COPD, n (%)	10 (16)	6 (20)	4 (13)	0.731
Preoperative spirometry				
FVC (% predicted)	104 [93–117]	99 [79–117]	107 [96–118]	0.204
FEV1 (%)	96 [79–109]	90 [70–105]	105 [86–116]	0.061
FEV1/FVC	75 ± 12	77 ± 16	74 ± 9	0.75
KCO (% predicted)	74 [62–93]	69 [58–80]	86 [67–98]	0.086
ERV (% predicted)				

BMI body mass index, *MRC* Medical Research Council Scale, *MV* mechanical ventilation, *OLV* one lung ventilation, *VC* vital capacity, *FEV1* forced expiratory volume in the 1st second, *FVC* forced vital capacity, *MEF* maximal expiratory flow, *ERV* expiratory reserve volume

p values are referred to comparison between $PEEP_{INCREMENTAL}$ and $PEEP_{DECREMENTAL}$ group

[37–58] % to 33 [25–45]% in the $PEEP_{DECREMENTAL}$ group, (mean difference 22 [95% CI 18–26]%; $p < 0.001$ vs baseline). There was a reduction in shunt after intervention in 77% (23/30) of the patients in the $PEEP_{INCREMENTAL}$ versus 90% (27/30) in the $PEEP_{DECREMENTAL}$ group ($p = 0.17$ for comparison among groups).

Low V/Q decreased from 86 [37–150] mmHg to 55 [38–75] mmHg in the $PEEP_{INCREMENTAL}$ group ($p = 0.14$ vs baseline) and from 69 [23–144] mmHg to 57 [34–101] mmHg in the $PEEP_{DECREMENTAL}$ group ($p = 0.58$ vs baseline).

High V/Q mismatch was similar among the two groups. (Table 2).

3.3 Respiratory mechanics and gas exchange

During the OLV pre-intervention (at ZEEP), the ΔP did not differ between the two groups, with observations of 15 [14–19] cm H_2O for the $PEEP_{INCREMENTAL}$ and 14 [13–19] cm H_2O for the $PEEP_{DECREMENTAL}$ group. The PEEP titration procedure resulted in a similar "optimal" median level in the two groups ($PEEP_{INCREMENTAL}$: 8 [6–12] cm H_2O, range 4–16 cm H_2O; $PEEP_{DECREMENTAL}$: 8 [8–10] cm H_2O, range 6–12 cm H_2O; $p = 0.74$ for comparison) (Table 2, Fig. 3). Nevertheless, the ΔP was 10 [9–11] cm H_2O in the $PEEP_{INCREMENTAL}$ and 8 [7–11] cm H_2O in the $PEEP_{DECREMENTAL}$ group ($p = 0.03$; Table 2).

The energy load applied during the LRM in the $PEEP_{DECREMENTAL}$ group was 5.8 [4.7–7.1] J. The total energy load in the OLV post-intervention step was 1.175 [0.920–1.791] J in the $PEEP_{INCREMENTAL}$ and 1.484 [1.091–2.054] J in $PEEP_{DECREMENTAL}$ group ($p = 0.25$)].

Only the patients in the $PEEP_{DECREMENTAL}$ group experienced a significant increase in the PaO_2/FIO_2 ratio after intervention (from 140 [99–176] to 186 [152–243], $p < 0.001$). In the $PEEP_{DECREMENTAL}$ group the PaO_2/FIO_2 ratio increased significantly after intervention. There were no significant changes in $PaCO_2$ before or after intervention in both groups (Table 3).

Table 2 Mechanical ventilation variables and V/Q̇ measurement during the study period

Variable	TLV, after induction		OLV, prior to intervention		OLV, after intervention		TLV, End of surgery	
	$PEEP_{INCREMENTAL}$	$PEEP_{DECREMENTAL}$	$PEEP_{INCREMENTAL}$	$PEEP_{DECREMENTAL}$	$PEEP_{INCREMENTAL}$	$PEEP_{DECREMENTAL}$	$PEEP_{INCREMENTAL}$	$PEEP_{DECREMENTAL}$
Mechanical ventilation								
Paw (cm H_2O)	20 [15–23]	18 [14–20.5]	23 [19.5–27.5]	22 [20–26]	25.5 [22.2–30]	24 [23–29]	24.5 [20.7–28.2]	18 [14–20.5]
Plateau pressure (cm H_2O)	13 [10–15]	13 [10–15]	15 [14–19]	15 [14–19]	19 [17–22]	17.5 [15–21]	19 [16–22]	18 [15–20]
Driving Pressure (cm H_2O)	13 [10–15]	12 [10–16]	15 [14–19]	14 [13–19]	**10 [9–11]**	**8 [7–11]#***	10 [8–12]	9 [7–12]
PEEP (cm H_2O)	0	0	0	0	8 [6–12]	8 [8–10]	8 [6–12]	8 [8–10]
Tidal volume	440 [385–500]	440 [400–490]	315 [270–350]	310 [290–350]	315 [270–350]	310 [290–350]	440 [390–500]	440 [400–490]
Respiratory rate	14 [14–15]	14 [13–15]	16 [14–16]	16 [14–16]	16 [14.2–17.5]	16 [16–18]	16 [14–16]	16 [14–17]
Mechanical power (J/m)	10.8 [8.6–12.4]	9.5 [8.1–12.7]	5.6 [4.5–6.8]	5.8 [4.4–6.6]	**6.8 [5.4–8.8]***	**7.0 [5.9–8.6]***	12.8 [10.0–16.1]	13.3 [11.4–15.0]
V/Q̇ variables								
Shunt (%)	26.2 [21.8–32.9]	24.0 [16.1–33.1]	49.8 [39.0–55.0]	45.2 [37.5–58.1]	**34.9 [28.0–42.1]***	**33.1 [24.7–45.1]***	18.6 [9.0–25.2]	18.5 [9.8–22.6]
Low V/Q̇ (mmHg)	39 [17–65]	35 [23–71]	86 [37–150]	69 [23–144]	55 [38–75]	57 [34–101]	28 [22–70]	35 [24–72]
High V/Q̇ (mmHg)	11 [6–15]	11 [6–15]	13 [10–16]	11 [7–15]	13 [11–18]	13 [6.7–17]	12 [10–16]	12 [7–17]

Paw Peak airway pressure, *PEEP* positive end-expiratory pressure; *V/Q̇* = Ventilation/perfusion ratio

#$p < 0.05$ vs the other group, *$p < 0.05$ vs prior to intervention

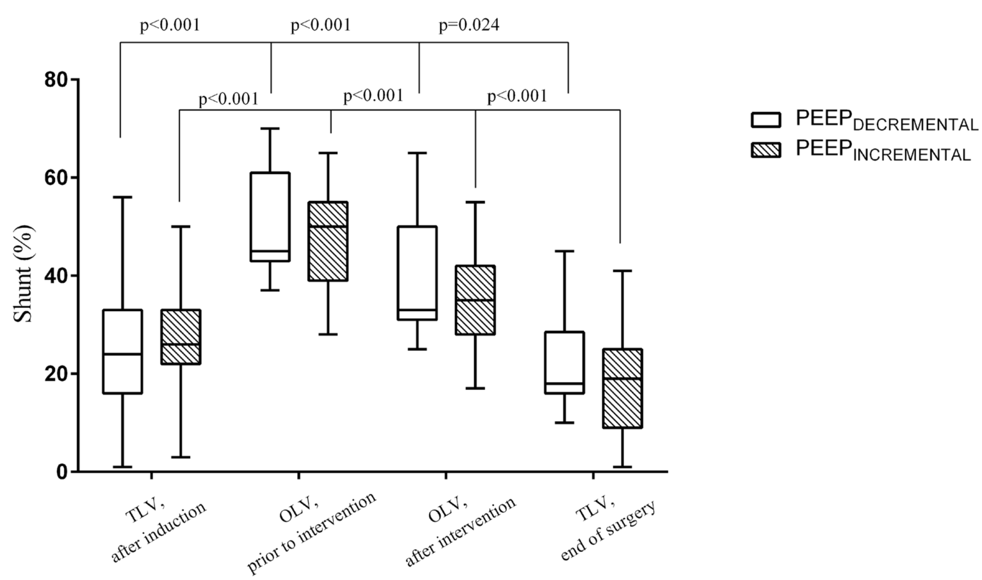

Fig. 2 Shunt evaluation during the study in the $PEEP_{INCREMENTAL}$ and $PEEP_{DECREMENTAL}$ group

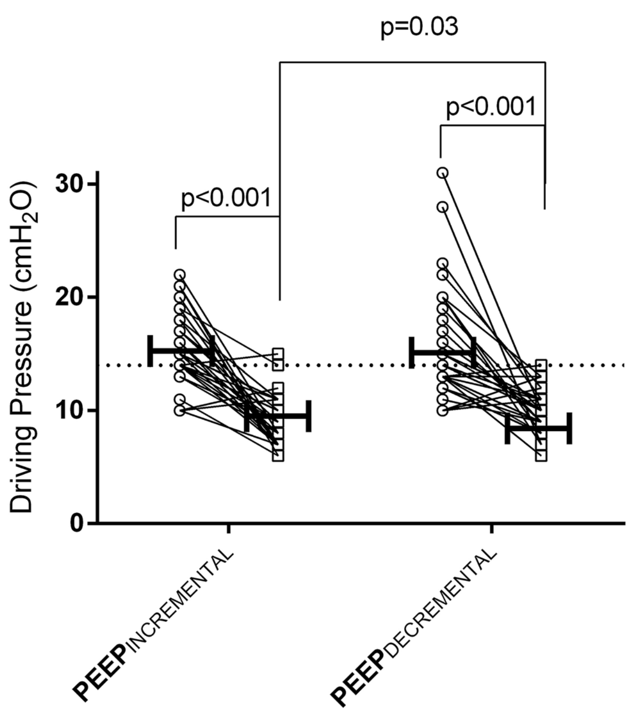

Fig. 3 Individual changes in driving pressure before and after the study intervention in the $PEEP_{INCREMENTAL}$ and $PEEP_{DECREMENTAL}$ group

3.4 Perioperative assessment

Intraoperative hemodynamic variables, as well as the number and kind of postoperative complications, are shown in Supplement Table 3. Patients in the two groups did not differ in terms of intraoperative management.

3.5 Post-hoc subgroups analysis

We performed various sub-group analyses to investigate whether different responses to the two PEEP titration strategies could be influenced by different clinical characteristics. No difference was found in $PEEP_{INCREMENTAL}$ or $PEEP_{DECREMENTAL}$ strategies when stratifying patients for age, BMI or history of COPD (Supplemental Fig. 2).

Among patients with $\Delta P > 14$ cm H_2O prior to intervention (n = 34), the reduction in ΔP was more pronounced in the $PEEP_{DECREMENTAL}$ group (from 19 [17–22] cm H_2O to 10 [8–11] cm H_2O) than in the $PEEP_{INCREMENTAL}$ one (from 18 [15–20] cm H_2O to 10 [9–12] cm H_2O), $p = 0.02$ for group comparison in favour of $PEEP_{DECREMENTAL}$ group).

4 Discussion

The main result of our study is that, among patients undergoing video-assisted thoracic surgery in OLV, an open lung approach strategy based on low TV combined with a ΔP-oriented *decremental* PEEP titration resulted in lower values of driving pressure and increase in oxygenation when compared to a $PEEP_{INCREMENTAL}$ strategy. However, both strategies were equally able to reduce shunt and driving pressure at the end of surgery.

Individualized PEEP has been shown to improve regional ventilation distribution and oxygenation and to decrease the incidence of postoperative atelectasis and PPCs in both abdominal [23] and thoracic surgery [4]. On the other hand, high intraoperative driving pressure has been found to be an independent predictor of PPCs [5, 6]. Combining these concepts, a ΔP-oriented PEEP setting has been recently proposed for patient undergoing OLV during thoracic surgery.

Table 3 Blood gas analysis during the study period

Variable	TLV, after induction		OLV, prior to intervention		OLV, after intervention		TLV, End of surgery	
	PEEP-INCREMENTAL	PEEP-DECREMENTAL	PEEP-INCREMENTAL	PEEP-DECREMENTAL	PEEP-INCREMENTAL	PEEP-DECREMENTAL	PEEP-INCREMENTAL	PEEP-DECREMENTAL
PaO_2/F_IO_2 ratio (mmHg)	350 [238–438]	298 [219–447]	139 [103–202]	140 [99–176]	153 [103–192]	**186 [152–243] #***	423 [241–492]	402 [262–463]
F_IO_2	50 [40–55]	40 [40–50]	58 [49–66]	55 [49–60]	**65 [56–73]***	**50 [40–52]#***	57 [50–65]	50 [44–60]
$PaCO_2$ (mmHg)	47 [42–51]	38 [42–52]	55 [50–59]	53 [49–60]	59 [54–62]	54 [51–64]	49 [45–52]	50 [43–53]
pH	7.36 ± 0.05	7.36 ± 0.05	7.31 ± 0.05	7.31 ± 0.07	7.27 ± 0.05*	7.28 ± 0.06*	7.31 ± 0.04	7.31 ± 0.06
HCO_3^-	26.9 ± 2.6	26.5 ± 2.5	27.0 ± 1.8	26.7 ± 2.3	26.4 ± 1.7	26.3 ± 2.5	24.7 ± 1.9	24.4 ± 2.3
Lactate (mmol/L)	1 [0.7–1.2]	0.8 [0.7–1.2]	0.8 [0.7–1.2]	0.8 [0.7–1.1]	0.8 [0.6–1]	0.8 [0.7–1.1]	0.9 [0.7–1.0]	0.8 [0.7–1.0]
Hb (g/dL)	12.6 ± 1.8	12.4 ± 1.6	12.1 ± 1.6	12.0 ± 1.6	12.1 ± 1.7	11.9 ± 1.6	12.0 ± 1.9	11.5 ± 1.7

Pa_{CO2} arterial partial pressure of carbon dioxide, Pa_{O2} arterial partial pressure of oxygen, F_IO_2 fraction of inspired oxygen, *Hb* hemoglobin

#p < 0.05 vs the other group, *p < 0.05 vs prior to intervention

However, there are at least two different approaches to PEEP setting in this context: the *incremental* or the *decremental* approach. We found that both approaches were able to reduce ΔP to "safe" levels [6, 21, 24], and that, surprisingly the PEEP levels needed to minimize the ΔP were similar in both groups (Table 2). However, the $PEEP_{DECREMENTAL}$ strategy resulted in the lowest intraoperative ΔP. These results gain clinical relevance due to the described relationship between intraoperative ΔP and postoperative outcomes [5, 6]. Our data confirm the results of recent studies on the effects of the open lung approach applied during OLV [8]. Rauseo and coworkers found that a $PEEP_{DECREMENTAL}$ strategy was able to decrease transpulmonary driving pressure and to improve oxygenation [8] and Ferrando and co-workers showed that a $PEEP_{DECREMENTAL}$ was able to preserve the improvement in static compliance obtained through a LRM [7]. This could explain our findings of a lower ΔP and of an improvement in oxygenation in the $PEEP_{DECREMENTAL}$ group. We hope that our physiological data could help to interpret the results of the clinical studies on PEEP setting during OLV. Indeed, in our study we reproduced the protocols of two recent randomized controlled trials, the Park study [4] and the ongoing PROTHOR trial [12].

One major concern is that the $PEEP_{DECREMENTAL}$ approach could critically decrease patient's cardiac output through both a *preload* and an *afterload* effect of the LRM needed to recruit the lungs before PEEP titration. However, the hemodynamic impact of the LRM during OLV has been previously shown to be mostly negligible [7, 8, 25, 26]. Some authors advocated the risk that the high amount of energy delivered to the lungs could result in alveolar hyperinflation and thus in a sort of unconscious "harmful" strategy [27, 28]. Nonetheless, in our patients we found that the mechanical power applied during the LRM was 5.8 [4.7–7.1] J, considerably lower than the "harmful" threshold of 25 J/min Joules suggested in patients with ARDS [29]. Additionally, the high V/Q fraction, a suitable surrogate of hyperinflation, was similar between the two groups (Table 2),

We also assessed the differential effects of the two strategies on the cohort of patients with higher baseline ΔP (i.e. higher than 14 cm H_2O) during OLV. This subgroup analysis showed that these patients had a greater decrease in ΔP and increase in PaO_2/FIO_2 ratio when randomized to the $PEEP_{DECREMENTAL}$ group as compared to the $PEEP_{INCREMENTAL}$ one. Thus, despite our data should be extrapolated to the clinical context with caution, we speculate that patients with more compromised oxygenation and lung mechanics could be the best candidate to the $PEEP_{DECREMENTAL}$ strategy.

Our study has some limitations. First of all, our results could have been influenced by the effects of the LRM, which was performed only in the $PEEP_{DECREMENTAL}$ group. However, we would like to point out that the LRM is part of the open lung approach [30] and thus it is impossible to differentiate the role of PEEP and LRM in our $PEEP_{DECREMENTAL}$ group. On the other hand, since we were interested in reproducing the $PEEP_{INCREMENTAL}$ strategy proposed in the Park's clinical trial [4], we did not apply any LRM in the $PEEP_{INCREMENTAL}$ group. Secondly, our study was not powered to investigate clinical outcomes of such PPCs. Thirdly, we did not record advanced hemodynamic parameters and, thus, we cannot report on the differential impact of the two strategies. However, previous studies have shown that both PEEP and LRM have slight and transient effects on cardiac output during OLV [25, 26]. Lastly, we used the PaO_2/FIO_2 ratio as index of oxygenation but applied a fixed FIO_2 in the two groups, and this could have partially influenced our results [20].

In conclusion, we have shown the beneficial physiological effects of two ΔP-oriented PEEP titration strategies during OLV. According to our data, as compared with an incremental PEEP titration approach, decremental PEEP titration immediately after a LRM was more effective in decreasing ΔP and improving oxygenation, particularly in patients with higher (i.e. > than 14 cm H_2O) intraoperative ΔP.

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Compliance with ethical standards

Conflict of interest None of the authors received compensation to perform this study. Dr. Rees is a board member and minor shareholder of Mermaid Care A/S (Nørresundby, Denmark), who commercially produces the ALPE system. Dr. Karbing has performed consultancy work for Mermaid Care A/S. The remaining authors declare no competing interests.

Ethical approval The trial was approved by the Ethics Committee of our institution (protocol No. 11072017).

Informed consent Informed consent was obtained from each patient before surgery.

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