

Physiologic Evaluation of Ventilation Perfusion Mismatch and Respiratory Mechanics at Different Positive End-expiratory Pressure in Patients Undergoing Protective One-lung Ventilation

Savino Spadaro, M.D., Ph.D., Salvatore Grasso, M.D., Ph.D., Dan Stieper Karbing, Ph.D., Alberto Fogagnolo, M.D., Marco Contoli, M.D., Giacomo Bollini, M.D., Riccardo Ragazzi, M.D., Gilda Cinnella, M.D., Marco Verri, M.D., Narciso Giorgio Cavallesco, M.D., Stephen Edward Rees, Ph.D., Dr.tech., Carlo Alberto Volta, M.D.

ABSTRACT

Background: Arterial oxygenation is often impaired during one-lung ventilation, due to both pulmonary shunt and atelectasis. The use of low tidal volume (V_T) (5 ml/kg predicted body weight) in the context of a lung-protective approach exacerbates atelectasis. This study sought to determine the combined physiologic effects of positive end-expiratory pressure and low V_T during one-lung ventilation.

Methods: Data from 41 patients studied during general anesthesia for thoracic surgery were collected and analyzed. Shunt fraction, high \dot{V}/\dot{Q} and respiratory mechanics were measured at positive end-expiratory pressure 0 cm H₂O during bilateral lung ventilation and one-lung ventilation and, subsequently, during one-lung ventilation at 5 or 10 cm H₂O of positive end-expiratory pressure. Shunt fraction and high \dot{V}/\dot{Q} were measured using variation of inspired oxygen fraction and measurement of respiratory gas concentration and arterial blood gas. The level of positive end-expiratory pressure was applied in random order and maintained for 15 min before measurements.

Results: During one-lung ventilation, increasing positive end-expiratory pressure from 0 cm H₂O to 5 cm H₂O and 10 cm H₂O resulted in a shunt fraction decrease of 5% (0 to 11) and 11% (5 to 16), respectively ($P < 0.001$). The P_{aO_2}/F_{iO_2} ratio increased significantly only at a positive end-expiratory pressure of 10 cm H₂O ($P < 0.001$). Driving pressure decreased from 16 ± 3 cm H₂O at a positive end-expiratory pressure of 0 cm H₂O to 12 ± 3 cm H₂O at a positive end-expiratory pressure of 10 cm H₂O ($P < 0.001$). The high \dot{V}/\dot{Q} ratio did not change.

Conclusions: During low V_T one-lung ventilation, high positive end-expiratory pressure levels improve pulmonary function without increasing high \dot{V}/\dot{Q} and reduce driving pressure. (ANESTHESIOLOGY 2018; XXX:00-00)

ARTERIAL oxygenation is impaired during one-lung ventilation (OLV) in lateral decubitus due to the obligatory shunt through the nondependent lung.^{1,2} The generation of atelectasis in the dependent, ventilated lung further decreases oxygenation by reducing the aerated lung volume and inducing ventilation-perfusion mismatch.^{3,4} Applying a positive end expiratory pressure (PEEP) to the dependent lung could ameliorate intrapulmonary shunt.^{2,4-6} However, studies have shown conflicting results, with some showing sustained improvement⁵⁻⁸ and others showing no effects⁹ or even worsening of oxygenation.^{10,11} These conflicting results might be at least partially explained by the different interplay between PEEP and tidal volume (V_T) in the different studies. Indeed, the previous quoted studies report the use of different V_T during OLV, ranging between 6 and 10 ml/kg. High V_T have per

What We Already Know about This Topic

- Low tidal volume is necessary to prevent lung injury during one-lung anesthesia but can potentiate development of atelectasis. Although positive end-expiratory pressure can reduce atelectasis, it may cause hyperinflation and increased alveolar dead space.

What This Article Tells Us That Is New

- Shunt fraction and ventilation/perfusion ratio (\dot{V}/\dot{Q}) distribution was measured in 41 patients undergoing one-lung anesthesia. Positive end-expiratory pressure at 5 or 10 cm H₂O, applied in random order, resulted in lower shunt fraction and driving pressure, without increasing dead space.

se the potential of decreasing shunt by recruiting the atelectatic lung areas, but this strategy may be deleterious, both causing

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lung injury^{12,13} and augmenting cytokine production.^{12,13} Thus, considerable attention has been paid to identify the correct V_T to be used during OLV,^{13–16} and recent evidence suggests that a lung protective tidal volume of 4 to 5 ml/kg predicted body weight (PBW) should be applied during OLV.¹⁶

Because atelectasis more likely occurs with low V_T ,¹⁷ the aim of our study was to investigate whether higher PEEP during low V_T OLV can improve both oxygenation through reduction in shunt and lung mechanics through reduced driving pressure. Thus, we applied different PEEP levels (0, 5, and 10 cm H₂O) and measured ventilation/perfusion matching and respiratory mechanics in patients undergoing thoracoscopic surgery ventilated with a V_T of 4 to 5 ml/kg PBW during OLV. We therefore sought to describe the physiologic effects of increased PEEP.

Materials and Methods

This study was performed in the Department of Anesthesia and Intensive Care at the University Hospital of Ferrara (Italy) from January to November 2016. Our trial was approved by the Ethics Committee of our institution (protocol No. 140495) and registered in Clinicaltrials.gov (trial No. NCT02968550). Written informed consent was obtained from each patient before surgery.

Patients scheduled for elective lobectomy or lung resection through video-assisted thoracoscopic surgery requiring OLV and lateral position were enrolled if they were more than 18 yr of age and with an American Society of Anesthesiologists Physical Status I to III. Patients were excluded in case of hemodynamic instability (defined as a decrease in systolic arterial pressure of more than 20% from baseline), severe chronic respiratory failure (chronic obstructive pulmonary disease patients with Global Initiative for Obstructive Lung Disease stage 3 or 4,¹⁸ preoperative hemoglobin less than 10 g ml⁻¹), or procedures requiring unplanned conversion to thoracotomy surgery or planned to be shorter than 30 min.

As a routine practice in our institution, patients underwent preoperative spirometry performed in sitting position according to the American Thoracic Society's standards, using SpiroPro spirometer (SpiroPro; Jaeger, Germany). Spirometry measurement of vital capacity, forced expiratory volume in the 1st second, forced vital capacity (FVC), expiratory reserve volume (ERV), and transfer coefficient (KCO) was performed. Before anesthesia induction, a thoracic epidural catheter (Tuohy; Braun Laboratories, Germany) was placed between T3 and T6 and 3 ml of bupivacaine 0.25% was administered.

All patients breathed an inspiratory oxygen fraction (F_{IO_2}) of 0.8 during the induction of general anesthesia to maintain

adequate oxygenation while reducing the risk of absorption atelectasis.¹⁹ Anesthesia was induced with propofol (1.5 to 2 mg/kg), fentanyl (3 µg/kg), and rocuronium (0.6 mg/kg) to facilitate tracheal intubation. The trachea was intubated with an appropriately sized and side double lumen tube (Broncho-part; Rush, Germany). Tube position was confirmed by bronchoscopy in the supine and lateral positions. Anesthesia was maintained with a continuous infusion of propofol (150 to 200 µg·kg⁻¹·min⁻¹), remifentanyl (0.1 to 0.2 µg·kg⁻¹·min⁻¹), and *cis*-atracurium (2 µg·kg⁻¹·min⁻¹). Balanced crystalloid solutions²⁰ were infused at a rate of 3 ml·kg⁻¹·h⁻¹.

Patients were ventilated with a square flow waveform using Dräger Primus ventilator (Drägerwerk AG and Co. KGaA, Germany). During two-lung (bilateral) ventilation, V_T was set to 6 to 8 ml/kg PBW and zero PEEP. During OLV, V_T was reduced to 4 to 5 ml/kg PBW, and PEEP varied from 0 to 10 cm H₂O, according to the experimental protocol (see Study Protocol). F_{IO_2} was set to maintain peripheral oxygen saturation (SpO₂) equal to or greater than 92%. The inspiratory-to-expiratory ratio was set to 1:2, and frequency was adjusted to maintain an arterial PaCO₂ between 40 and 60 mmHg.

Respiratory mechanics were assessed by the constant V' /rapid occlusion method previously described in detail.²¹ End-inspiratory occlusion was obtained by increasing end-inspiratory pause to 40%. Driving pressure (ΔP) was calculated as plateau pressure – PEEP, whereas respiratory system compliance (C_{RS}) was calculated as V_T /(end-inspiratory plateau pressure – PEEP).

Patients were monitored using a Dräger Infinity C700 monitor (Dräger Medical, Germany) with an electrocardiogram, pulse oximetry, end-tidal carbon dioxide, and continuous arterial pressure monitoring *via* a catheter inserted into the radial artery. The latter was placed under local anesthesia before induction of general anesthesia, in line with the standard practice of our institution, for invasive blood pressure and to obtain samples for blood gas monitoring. Analysis of arterial blood gases were performed within 3 min from sampling (Cobas 123 POC; Roche Diagnostics, Switzerland). Depth of anesthesia was monitored using bispectral index (Aspect A-2000; Aspect Medical System, USA).

Shunt and ventilation/perfusion ratio (\dot{V}/\dot{Q}) matching were assessed by the ALPE system (ALPE Integrated, Mermaid Care A/S, Denmark). To assess \dot{V}/\dot{Q} matching, the ALPE system instructs the user to modify F_{IO_2} in three or four steps. At each F_{IO_2} level, the ALPE system identifies steady state and measures ventilation, SpO₂, oxygen consumption, CO₂ production, and inspiratory and expiratory fractions of O₂ and CO₂. These measurements are taken automatically by inserting a sampling tube in the respiratory circuit for measurement of flow, O₂, and CO₂ and by placing the pulse oximeter on a finger. In addition, the system estimates the acid–base and oxygenation status including arterial PaCO₂, taking into account the results of an arterial blood gas sample. These parameters are then used to identify the fractions of ventilation and perfusion in a three-compartment model of the lung, including two ventilated and perfused compartments and a further perfused-only

of Emergency and Organ Transplant, Aldo Moro University of Bari, Bari, Italy (S.G.); Respiratory and Critical Care Group, Department of Health Science and Technology, Aalborg University, Aalborg, Denmark (D.S.K., S.E.R.); Research Centre on Asthma and Chronic Obstructive Pulmonary Disease, Department of Medical Sciences, University of Ferrara, Ferrara, Italy (M.C.); and Department of Anesthesia and Intensive care, University of Foggia, Foggia, Italy (G.C.).

compartment, describing pulmonary shunt. The model takes into account also some extrapulmonary factors including acid–base status, hemoglobin concentration, the nonlinearity of hemoglobin oxygen binding, cardiac output, and the measured oxygen consumption. The system assumes a cardiac index of $3.7 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, as previously reported in intensive care patients.²² Body surface area was calculated from height and weight as previously performed by Gehan and George.²³ The estimation of ventilation and perfusion parameters is performed as follows. It is well known that variation in F_{IO_2} can be used to identify shunt, with oxygenation problems at $F_{\text{IO}_2} = 1$ being due to shunt alone. Because F_{IO_2} values of 1 may increase the risk of absorption atelectasis²⁴ and may therefore be undesirable, the ALPE algorithm applies the principle that in the case of true pulmonary shunt, SpO_2 will change little when changing F_{IO_2} . This is in contrast to areas with low \dot{V}/\dot{Q} , where SpO_2 will change greatly with F_{IO_2} . Accordingly, through variation of F_{IO_2} in three or four steps, the system mathematically estimates shunt and low \dot{V}/\dot{Q} ratios. Further, the ALPE algorithm takes into account the end-tidal to arterial CO_2 gradient to account for the part of this gradient due to shunt and low \dot{V}/\dot{Q} and the one due to high \dot{V}/\dot{Q} ratio. For ease of understanding, the estimates of ventilation and perfusion obtained from ALPE analysis are converted into indices describing low and high \dot{V}/\dot{Q} regions. Low \dot{V}/\dot{Q} mismatch is represented as the difference in O_2 partial pressure between end-tidal gas and blood leaving lung capillaries in the low \dot{V}/\dot{Q} areas. As an example, a low \dot{V}/\dot{Q} index of 10 kPa indicates the need for an increase in F_{IO_2} of approximately 10% to counter the effect of low \dot{V}/\dot{Q} on oxygenation of nonshunted blood.

High \dot{V}/\dot{Q} mismatch is represented as an index constituting the difference in CO_2 partial pressure between end-tidal gas and blood leaving lung capillaries. A high \dot{V}/\dot{Q} index of more than 0 kPa can be interpreted as insufficient removal of CO_2 due to high \dot{V}/\dot{Q} . The ALPE technique has been validated and applied in varied patient populations.^{25–28}

Study Protocol

Measurements were made (1) before surgery, when patients were ventilated at zero PEEP during bilateral lung ventilation in the supine position (TLV baseline), and (2) during OLV in the lateral decubitus, after collapse of the nondependent lung. OLV (fig. 1) immediately opened the lumen of the endotracheal tube of the nonventilated lung to room air. After the assessment of shunt, respiratory mechanics, and gas exchange at ZEEP, we applied in random order 5 and 10 cm H_2O of PEEP. Randomization was obtained by using a computer-generated number. Each level of PEEP was maintained for 15 min, allowing the effects of PEEP to reach an equilibrium.²⁹ Parameters describing respiratory mechanics, hemodynamics, and gas exchange were measured at each PEEP step. The design of the study is summarized in figure 1.

Statistical Analysis

Normal distribution of data was tested by the Shapiro–Wilk normality test. The data are reported as means \pm SD or median (interquartile range) as appropriate. Differences between measurements at different PEEP levels were analyzed using repeated measure ANOVA or Friedman’s rank analysis for normally or not normally distributed variables,

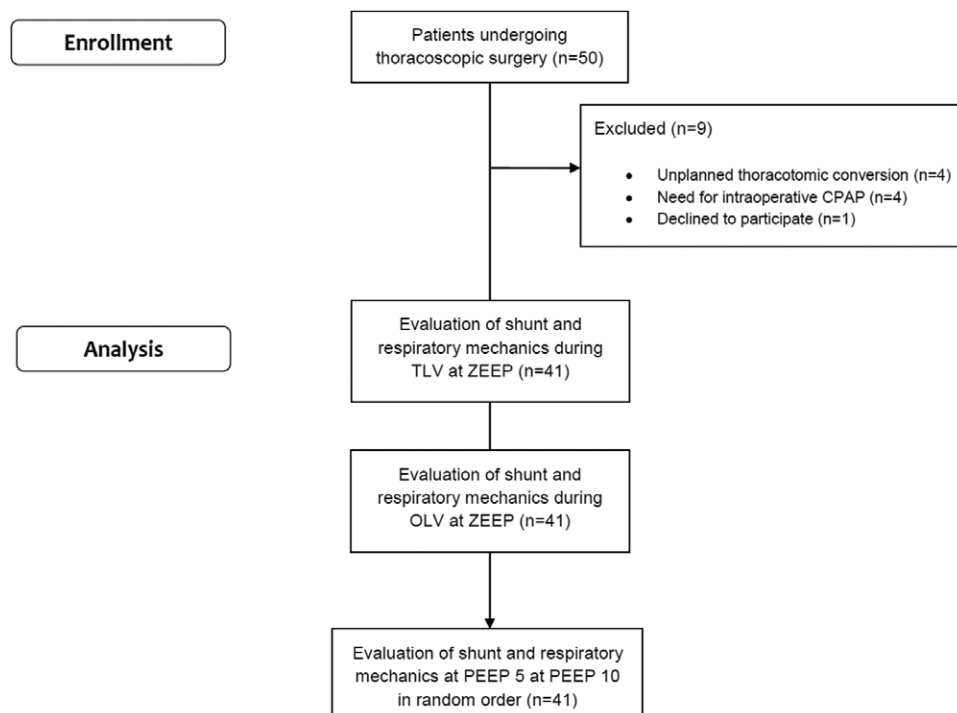


Fig. 1. Flowchart of the study. CPAP = continuous positive airway pressure; OLV = one-lung ventilation; PEEP = positive end-expiratory pressure; TLV = two-lung ventilation ZEEP = zero positive end-expiratory pressure.

respectively. When multiple comparisons were made, *p* values were adjusted by the Bonferroni *post hoc* procedure. The treatment effect is expressed as mean difference and 95% CI or median difference (interquartile range). Pearson correlation with R square was used to analyze the correlation. Correlation strength was considered based on the absolute value of the *r* (0.20 to 0.39 “weak,” 0.40 to 0.59 “moderate,” and 0.60 to 0.79 “strong”).³⁰ All the analyses performed for the primary and secondary outcomes were preplanned; furthermore, a *post hoc*, subgroup analysis was performed to describe the behavior of physiologic variables, after identification of a subgroup of patients where ΔP did not decrease with increased PEEP. Two-tailed statistical hypothesis testing was performed with *P* values of ≤ 0.05 considered statistically significant. Statistical analysis was performed with using SPSS Statistics for Windows, version 20.0 (IBM, USA). This is the primary analysis of these data.

Sample Size Calculation

An *a priori* sample size was calculated according to the primary endpoint: the improvement in shunt fraction by increasing PEEP levels in patients undergoing OLV in lateral decubitus. Based on at least 90% power, 40 patients were required to detect a mean difference in shunt fraction from 38 ± 5 to $34 \pm 7\%$ after the application of 5 cm H₂O of PEEP using paired *t* tests with an $\alpha = 0.05$. This is consistent with the observed difference in shunt fraction seen previously when investigating the effects of PEEP during OLV at a V_T of 10 ml/kg.⁸ Finally, 50 patients were required to account for an anticipated dropout of 20% due to declining participation, interruption of intervention, and unplanned thoracotomy conversion. Sample size analysis was performed using MedCalc software (version 9.3.6.0; MedCalc, Belgium).

Results

Study Population

Among the 50 patients assessed for eligibility, 41 completed the study (figure 1); their clinical and demographic characteristics are described in table 1. There were no missing data in the data set. The median shunt during TLV at zero PEEP was 19% (9 to 23) with a C_{RS} of 36.2 ± 10 ml/cm H₂O and a ΔP of 13 ± 4 cm H₂O. The average shunt raised to 33% (27 to 45) during OLV at ZEEP, whereas C_{RS} to 22 ± 5 ml/cm H₂O and ΔP increased to 16 ± 3 cm H₂O. Hemodynamic parameters did not change throughout the protocol, irrespective of the applied PEEP level (table 2).

Effects of PEEP on Ventilation/Perfusion and Respiratory Mechanics (Table 2)

The median decrease in shunt fraction was 5% (0 to 11) at PEEP 5 cm H₂O and 11% (5 to 16) at PEEP 10 cm H₂O ($P < 0.001$), whereas the C_{RS} increased by 3 ml/cm H₂O (CI 1.4 to 4.6) at PEEP 5 cm H₂O and 6.7 ml/cm H₂O (CI 4.7 to 8.5) at PEEP 10 cm H₂O ($P < 0.001$). Similarly, ΔP decreased

Table 1. Patient Characteristics

Variable	Patients n = 41
Age (yr)	68 (60–74)
BMI (kg/m ²)	26 ± 4
ASA score, n	
II	10
III	31
MRC dyspnea scale	2 (1.5–3)
Sex (male/female), n	30/11
Surgery side (left/right)	23/18
Type of surgery, n	
Lobectomy	24
Wedge resection	17
Duration of MV (min)	236 ± 36
Duration of OLV (min)	216 ± 33
Comorbidities	
Diabetes, n (%)	9 (22)
Cardiac dysfunction, n (%)	21 (51)
COPD, n (%)	7 (17)
Smoking history	38 (93)
Pack years	18 (14–23.5)
Current smokers, n (%)	21 (49)
Preoperative spirometry	
VC (% predicted)	97 (84–113)
KCO (% predicted)	70 (51–87)
FEV ₁ (% predicted)	92 (81.4–105.4)
FVC (% predicted)	97 (85–111)
FVC/VC	0.99 (0.94–1)
FEV ₁ /FVC	74 (68.3–79.9)
ERV (% predicted)	86 (60–123)

Current smoking was defined as at least 1 yr from quitting.

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ERV = expiratory reserve volume; FEV₁ = forced expiratory volume in the 1st second; FVC = forced vital capacity; KCO = transfer coefficient; MRC = Medical Research Council; MV = mechanical ventilation; OLV = one-lung ventilation; VC = vital capacity.

from 16 ± 3 cm H₂O to 14 ± 3 cm H₂O at PEEP 5 and to 12 ± 3 cm H₂O at PEEP 10; $P < 0.001$ (fig. 2). High \dot{V}/\dot{Q} ratio was not significantly different between TLV and OLV, regardless of the PEEP level (table 2). We found a tendency for high \dot{V}/\dot{Q} to increase at PEEP 10 cm H₂O in those patients where ΔP increased with PEEP (Supplemental Digital Content 1, <http://links.lww.com/ALN/B572>). The P_{aO_2}/F_{iO_2} ratio increased significantly only at PEEP 10 cm H₂O compared to zero PEEP (281 (129 to 243) mmHg *versus* 142 (96 to 168) mmHg; $P < 0.001$).

Predictors of Shunt Severity during OLV

There was a strong inverse correlation between ERV and the amount of shunt developed during OLV at ZEEP ($r = -0.79$; $r^2 = 0.62$; $P < 0.001$) (fig. 3). A similar but weaker correlation was found at PEEP 5 ($r = -0.72$; $r^2 = 0.52$; $P < 0.001$) (Supplemental Digital Content 2, <http://links.lww.com/ALN/B573>) and PEEP 10 ($r = -0.58$; $r^2 = 0.40$; Supplemental Digital Content 3, <http://links.lww.com/ALN/B574>). Furthermore, there was a moderate correlation between KCO and shunt

Table 2. Intraoperative Variables

Variable	TLV	PEEP 0	PEEP 5	PEEP 10
Shunt fraction (%)	19 (9–23)	33 (27–45)	31 (22–42)*	22 (14–29)*†
Low \dot{V}/\dot{Q} (mmHg)	31 (22–49)	47 (28–112)	45 (22–88)	38 (24–90)
High \dot{V}/\dot{Q} (mmHg)	13±4	13±5	13±5	14±6
C_{RS} (ml/cm H ₂ O)	36.2±10	22.0±5	25.5±7*	29.5±8*†
ΔP (cm H ₂ O)	13±4	16±3	14±3*	12±3*†
V_T (ml/kg)	7±0.6	4.9±0.5	5±0.4	4.8±0.5
RR (breath/min)	13±1	14±2	15±2	15±2
Arterial pH	7.35±0.1	7.32±0.01	7.31±0.01	7.30±0.1
Paco ₂ (mmHg)	46±6	48±7	50±6	51±8
Pao ₂ /Fio ₂ ratio (mmHg)	303 (150–351)	142 (96–168)	158 (107–205)	281 (129–243)*†
Mean arterial pressure (mmHg)	82±16	76±18	77±19	77±18
Heart rate (beats/min)	77±10	69±11	70±12	68±10

C_{RS} = respiratory system compliance; Fio₂ = fraction of inspired oxygen; ΔP = driving pressure; PEEP = positive end expiratory pressure; RR = respiratory rate; TLV = two-lung ventilation; \dot{V}/\dot{Q} = ventilation/perfusion ratio; V_T = tidal volume.

* $P < 0.05$ compared to PEEP 0. † $P < 0.05$ compared to PEEP 5 (repeated measure ANOVA or Friedman’s rank analysis, both with multiple pairwise comparisons and Bonferroni correction, comparing different PEEP levels during OLV).

($r = -0.47$; $r^2 = 0.23$; $P = 0.04$) and a weak correlation between body mass index ($r = 0.33$; $r^2 = 0.12$; $P = 0.03$) and shunt.

Discussion

The main finding of this study is that a PEEP of 10 cm H₂O is needed to decrease the shunt fraction and the driving pressure while increasing oxygenation in patients ventilated with “protective” low V_T during OLV. In patients undergoing general anesthesia and muscle paralysis, the decrease of FRC associated with the development of atelectasis impairs the matching of ventilation and perfusion. During OLV, the absence of ventilation in the nondependent lung and the atelectasis induced by anesthesia in the dependent lung result in further ventilation/perfusion mismatch and hypoxia. However, no conclusive data are available on the correct amount of PEEP that should be applied during OLV to ameliorate oxygenation. This probably reflects the fact that shunt is highly influenced by the ventilatory pattern and in particular by the interplay between V_T and PEEP.¹⁵ The recent extension

of the “lung protective ventilation” concept from the ARDS to the anesthesia field underlines the need for minimizing both atelectasis and overdistension,³¹ suggesting the use of low V_T and a “adequate” PEEP levels. However, OLV might deserve even lower V_T as compared to those recommended for protective ventilation during TLV.^{13,16} In thoracic surgery, a V_T of 5 ml/kg was shown to decrease postoperative levels of tumor necrosis factor- α , interleukin-8, and interleukin-10 as compared to 10 ml/kg.¹³ Of note, in an animal study, a V_T of 10 ml/kg compared to one of 5 ml/kg resulted in inhomogeneous distribution of aeration predisposing to postoperative lung injury.¹⁴ The role played by low V_T during OLV is further supported by a study from Qutub *et al.*³² demonstrating higher extravascular lung water with a V_T of 8 or even 6 ml/kg as compared to a V_T of 4 ml/kg. Hence, as suggested by Lohser and Slinger,¹⁶ the adequate V_T during OLV should be around 4 or 5 ml/kg PBW. However, the use of low V_T may exacerbate the atelectasis in the dependent, ventilated lung. In patients with acute lung injury, Cereda

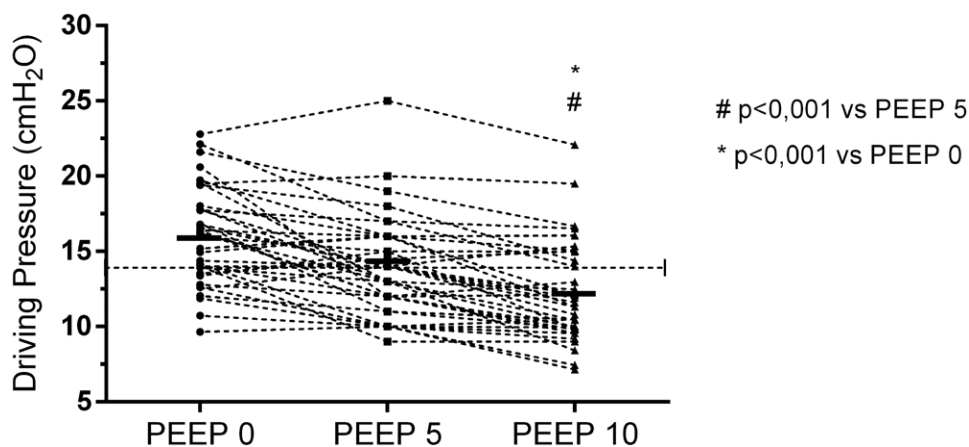


Fig. 2. Individual differences in driving pressure at different levels of positive end-expiratory pressure (PEEP). The horizontal dashed line shows the cutoff of 14 cm H₂O. The continuous horizontal lines show the means in each group.

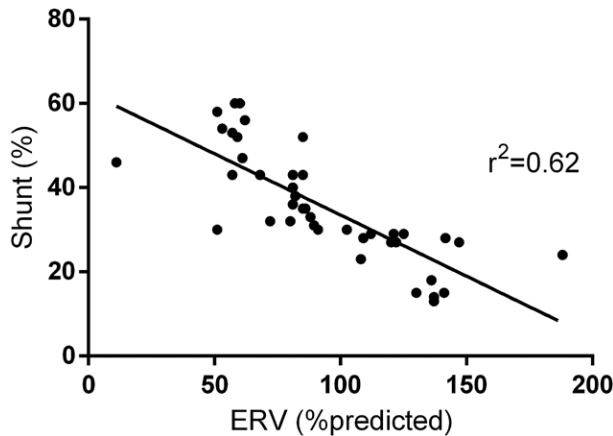


Fig. 3. Correlation between expiratory reserve volume (ERV) and intrapulmonary shunt measured at zero positive end-expiratory pressure.

*et al.*³³ demonstrated that low V_T could induce a progressive decrease in compliance, which could be prevented by setting an adequate PEEP level. Indeed, the use of low V_T without setting an appropriate PEEP level could likely exacerbate atelectasis and favor postoperative pulmonary complications (PPC).^{3,34–36}

Our results suggest that 10 cm H₂O of PEEP are needed when a V_T of 4 to 5 ml/kg is used. Indeed, 5 cm H₂O of PEEP were not able to improve oxygenation or to reduce both shunt and driving pressure (table 2). Recently, Neto *et al.*³⁷ demonstrated that the higher the intraoperative driving pressure, the greater the incidence of PPC, and this is likely true also in patients undergoing thoracic surgery.³⁶ Of note, a relatively high percentage of our patients (65%) had a value of ΔP higher than 14 cm H₂O during OLV at zero PEEP, and recent studies described a significant association between this ΔP cutoff and mortality in patients with ARDS.³⁸ Because in our patients 10 cm H₂O of PEEP applied during OLV decreased ΔP from 16 ± 3 cm H₂O to 12 ± 3 cm H₂O ($P < 0.001$) and decreased the percentage of patients with a ΔP level of more than 14 cm H₂O (29%), we speculate that the combination of low V_T and relatively high PEEP levels during OLV could be beneficial in reducing PPC. However, our physiologic study was not designed to investigate the impact of the ventilator strategy on clinical outcomes, and further studies are needed to confirm this hypothesis.

One may argue that, despite the low V_T , the application of PEEP can overdilate the lung parenchyma during OLV. In our study, we measured the high \dot{V}/\dot{Q} , as a marker of hyperinflation³⁹ and found that it did not change neither at PEEP 5 or 10 cm H₂O (table 2). This indicates that PEEP 10 cm H₂O, when associated with low V_T , does not result in an increase in dead space ventilation. Based on these data, we speculate that PEEP did not cause alveolar hyperinflation in our patients. However, hyperinflation, as commonly defined in the ARDS literature, is usually assessed using CT Hounsfield units and the relationship between hyperinflation and

physiologic dead space ventilation (West zone 1).⁴⁰ Interestingly, we recorded a nonsignificant trend for PEEP-induced increase in high \dot{V}/\dot{Q} ratio only in the few patients (6/41; 15%) in which the driving pressure did not decrease by increasing PEEP (Supplemental Digital Content 1, <http://links.lww.com/ALN/B572>). The lack of positive physiologic response in patients where driving pressure did not decrease by increasing PEEP was also seen in shunt, where the median value changed little on increasing PEEP (PEEP 0: 32% [29 to 45]; PEEP 5: 33% [22 to 40]; PEEP 10: 28% [22 to 34]).

Because patients undergoing thoracic surgery can have very different levels of shunt, usually ranging between 20 and 30%,^{41,42} we investigated the possible preoperative determinants of shunt to predict a higher risk of intraoperative hypoxia. Interestingly, we found a strong negative correlation ($r = -0.79$; $r^2 = 0.62$) between the preoperative ERV and the shunt fraction (fig. 3). This was not true for other spirometry parameters, such as forced expiratory volume in the 1st second, FVC, and Tiffenau Index, whereas other clinical or spirometry variables showed only weak (body mass index and FVC/vital capacity) to moderate (KCO) predicting values for intraoperative shunt. The relationship between preoperative ERV and intraoperative shunt can be explained by two factors. First, it is known that FRC and hence ERV are reduced during induction of anesthesia.⁴³ Second, a preexisting low ERV would therefore be reduced further during anesthesia and may result in an FRC below closing volume. Rothen *et al.*⁴⁴ previously demonstrated that pulmonary shunt is increased when the closing volume is greater than FRC. PEEP should increase ERV above closing volume reducing shunt and as a consequence weaken the relationship between preoperative ERV and perioperative shunt as observed in this study (Supplemental Digital Content 2 [<http://links.lww.com/ALN/B573>] and 3 [<http://links.lww.com/ALN/B574>] show the relationship between ERV and shunt at PEEP 5 and 10 cm H₂O, respectively).

Our study has some limitations. First, although the overall shunt levels were similar to those previously reported in the literature,⁴² this was a single-center study, and thus our results may be dependent on local surgical and anesthesiological practice. Second, the technique for assessing ventilation perfusion matching used in the present study employs a three-compartment lung model. This model has been shown to be a substantial improvement in describing data when compared to oxygenation indices such as the P_{aO_2}/F_{iO_2} ⁴⁵ but does not include the complexity of the 50 compartments model used in the multiple inert gas elimination technique (MIGET), the reference method for assessing gas exchange.⁴⁶ Though this technique is simpler than the reference one,⁴⁶ it has been shown to provide a good fit to MIGET data^{47,48} and to simulate arterial oxygenation with accuracy comparable to the MIGET model.⁴⁸ Accordingly, considering that the MIGET technique is costly for routine clinical use,⁴⁹ the presented technique could be regarded as suitable for bedside estimation of the \dot{V}/\dot{Q} ratio. Although the model used here accounts for several extrapulmonary parameters, cardiac output (CO) was not

measured, and the system assumes a fixed cardiac index. This may be a potential source of errors in the calculation of pulmonary shunt in our patients, because PEEP may impact on CO with several mechanisms, for example by decreasing the cardiac preload or by increasing right ventricular afterload. However, previous studies have showed no significant changes in CO after the application of PEEP in the dependent lung during OLV,^{8,50,51} and even aggressive recruitment maneuvers have been shown to have slight and transient effects on CO in this context.^{7,52} Furthermore, a previous validation study of this model showed that its estimate of shunt varies by an average of 2% per liter of CO change.⁵³ It should also be noted that the high \dot{V}/\dot{Q} values reported in table 2 represent a functional description of the gas exchange at the lung level rather than an anatomical description, which is usually derived from CT measurements.⁴⁰ Finally, although our results showed positive short-term physiologic effects of increasing PEEP, further studies are required to see whether the application of protective OLV combined with a PEEP of 10 cm H₂O would translate to improved postoperative outcome or whether an even higher PEEP level might be beneficial in some patients.

In conclusion, this study has shown that when using low V_T during one-lung ventilation, it is important to apply a proper amount of PEEP to prevent intraoperative increases in driving pressure and intrapulmonary shunt. It is likely that a PEEP of 10 cm H₂O is required. Our results indicate that this level of PEEP could be applied without compromising high \dot{V}/\dot{Q} . These results are of potential clinical interest for designing lung-protective ventilatory protocols to be applied during OLV.

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Competing Interests

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 other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Spadaro: Sant'Anna Hospital, University of Ferrara, 8, Aldo Moro, 44121 Ferrara, Italy. savinospadaro@gmail.com. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY'S articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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