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Effect of combining a recruitment maneuver with protective ventilation on inflammatory responses in video-assisted thoracoscopic lobectomy: a randomized controlled trial

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Abstract

Background We hypothesized that the addition of a recruitment maneuver to protective ventilation (PVRM) would result in lower pulmonary and systemic inflammatory responses than traditional ventilation or protective ventilation (PV) alone in patients undergoing lung surgery.

Methods Sixty patients who underwent scheduled thoracoscopic lobectomy were randomly assigned to three groups: traditional ventilation, PV, or PVRM. Ventilations were performed using a tidal volume of 10 mL/kg for the traditional ventilation group and either 8 mL/kg (two-lung) or 6 mL/kg (one-lung, OLV) with a positive end-expiratory pressure of 5 cm H_2O for the PV and PVRM groups. The RM was performed 10 min after the start of OLV. Fiberoptic bronchoalveolar lavage (BAL) was performed twice in dependent and non-dependent lungs: before the start and immediately after the end of OLV. Blood samples were collected at the same time points. The levels of cytokines, including TNF-α, IL-1β, IL-6, IL-8, and IL-10, were measured.

Results After OLV, the level of TNF-α in the BAL fluid of dependent lungs was significantly higher in the PV than in the PVRM group ($P = 0.049$), whereas IL-1β, IL-6, IL-8, and IL-10 levels were not significantly different among the groups. In non-dependent lung BAL fluid, no cytokines were significantly different among the groups. After OLV, IL-10 serum levels were significantly higher in the traditional ventilation than in the PVRM group ($P = 0.027$).

Conclusions Lower inflammatory responses in the ventilated lung and serum were observed with PVRM than with traditional ventilation or PV alone. Larger multi-center clinical trials are warranted to confirm the effects of different ventilatory strategies on postoperative outcomes.

Keywords Bronchoalveolar lavage · Cytokines · Lung surgery · One-lung ventilation · Positive-pressure respiration

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Mechanical ventilation may cause pulmonary and systemic inflammatory responses in patients during lung surgery [1] due to pulmonary damage, pulmonary oxidative stress, or ischemia–reperfusion injury [2]. This inflammation has been associated with multi-organ dysfunction and mortality [1, 3]; adjusting the ventilatory strategy during one-lung ventilation (OLV) has been used as a preventative measure [4].

Traditionally, using a large, 8–10 mL/kg, tidal volume (TV) without peak end-expiratory pressure (PEEP) has been advocated to prevent atelectasis during OLV [5], but it has been associated with postoperative complications and mortality after lung surgery [4, 6] due to hyperinflation of the lung causing volutrauma, barotrauma, and lung inflammation [7]. Therefore, protective ventilation (PV), in which a 5–6 mL/kg small TV is combined with adequate PEEP, has been suggested to attenuate inflammatory responses [8].

Using a small TV results in less alveolar stretching, and an adequate level of PEEP maintains the end-expiratory lung volume and further reduces the potential of pulmonary injury attributable to repeated opening and closing of atelectatic regions [9]. However, it has also been demonstrated that in normal, non-injured lungs, PV produces contradictory results in terms of inflammatory responses and mortality [10–12].

Recently, a recruitment maneuver (RM) was suggested to overcome the possibility of lung collapse [13]. When the RM is combined with an adequate level of PEEP, it reverses anesthesia-induced atelectatic areas and stabilizes the newly opened pulmonary units, thereby increasing lung homogeneity [14]. However, the efficacy of implementing RMs remains unspecified [15, 16]. It is likely that the required high inspiratory pressure may precipitate lung over-distension, thereby redistributing pulmonary blood flow towards atelectatic regions, worsening gas exchange, and inducing an inflammatory response [17].

We hypothesized that the addition of an RM to a PV (PVRM) protocol would result in lower pulmonary and systemic inflammatory responses than PV alone or traditional ventilation in patients undergoing lung surgery.

Materials and methods

This randomized trial was approved by the Institutional Review Board of Seoul National University Hospital (ref: 1203-101-403) and registered at the ClinicalTrials.gov website (ref: NCT01630395, June 21, 2012). Written informed consent was obtained from all patients. The participants were aged 20–80 years, had an American Society of Anesthesiologists (ASA) physical status of 1 or 2, and were scheduled for elective lobectomy using video-assisted thoracoscopy under general anesthesia. Patients with heart failure with a New York Heart Association Functional Class > 2, a preoperative pulmonary function test of forced vital capacity (FVC) reduced < 50%, a forced expiratory volume in the first second (FEV_1) < 50% of the predictive value, pulmonary hypertension with mean pulmonary arterial pressure > 25 mmHg, coagulation disorders, acute pneumonia, extrapulmonary infections, previous treatment with corticosteroids within 3 months prior to the surgery, history of recurrent pneumothorax, or previous lung resection surgery were excluded.

The patients were randomly assigned in a 1:1:1 ratio to one of three groups using a computer-generated randomization table: the "traditional ventilation" group, the "PV" group, or the "PVRM" group. Random sequences of size 3 blocks that included A, B, or C were generated. The intraoperative mechanical ventilation procedure was performed according to group assignment.

A bispectral index sensor (BIS™ sensor; Covidien, Boulder, CO) was attached to the patient's forehead. Anesthesia was induced by administering propofol (4–5 μg/mL) and remifentanil (4 ng/mL) via a target-controlled intravenous infusion (Orchestra® Base Primea, Fresenius Vial, Brezins, France). Rocuronium (0.6 mg/kg) was administered intravenously to achieve neuromuscular blockade. Tracheal intubation was performed using a double-lumen tube of 35 to 39 Fr (Broncho-Cath®, Mallinckrodt Medical Ltd, Athlone, Ireland). The correct placement of the double-lumen tube was evaluated using a fiberoptic bronchoscope (BF-MP60, Olympus, Tokyo, Japan). A 20 G catheter was placed in the radial artery to continuously monitor arterial pressure and the cardiac index (FloTrac/Vigileo system, Edwards Lifesciences, Irvine, CA). A central venous catheter was placed in the internal jugular vein. Anesthesia was maintained using propofol (3.5–5 μg/mL) and remifentanil (2–4 ng/mL) via a target-controlled infusion. Vecuronium (1 mg) was administered intermittently to maintain neuromuscular relaxation. Lactated Ringer's solution was infused at 6 mL/kg/h during surgery, and 6% hydroxyethyl starch 130/0.4 (Voluven®, Fresenius Kabi Korea, Seoul, Korea) (3–5 mL/kg) was infused if the cardiac index was less than 2.5 L/min/m^2.

Two-lung ventilation was performed using pressure-controlled with FiO_2 of 0.5 via an anesthesia machine (GE Datex-Ohmeda S/5 Avance, Madison, WI, USA). In the traditional ventilation group, inspiratory pressure was adjusted for a TV of 10 mL/kg, and PEEP was not applied. In the PV and PVRM groups, inspiratory pressure was adjusted for a TV of 8 mL/kg, and a PEEP of 5 cm H_2O was applied. The predicted body weight was used to calculate the TV: 50 + 0.91 (height in cm—152.4) in men and 45.5 + 0.91 (height in cm—152.4) in women [15, 18]. The respiratory rate was adjusted to achieve an end-tidal CO_2 of 35–45 mmHg, and the inspiration-to-expiration ratio was maintained at 1:2.

OLV was performed using pressure-controlled and FiO_2 was initially applied at 1.0. In the traditional ventilation group, inspiratory pressure was adjusted for a TV of 10 mL/kg, and PEEP was not applied. In the PV and PVRM groups, inspiratory pressure was adjusted for a TV of 6 mL/kg, and a PEEP of 5 cm H_2O was applied. In all three groups, TV was reduced by 1 mL/kg if peak airway pressure was ≥ 30 cm H_2O or plateau pressure was ≥ 25 cm H_2O. FiO_2 was decreased by 0.2 until 0.5 was reached if oxygen saturation was ≥ 95% and increased by 0.2 until 1.0 was reached if oxygen saturation was < 95% or PaO_2 was < 80 mmHg.

An RM was performed only in the PVRM group. The RM was applied at 10 min after the start of OLV as follows [15]. The inspiration time was increased by 50%, and the respiratory rate was set at 12 per min. Peak inspiratory pressure (PIP) and PEEP were set at 30 cm H_2O and 10 cm H_2O, respectively, during the first set of three breaths; 35 cm

H_2O and 15 cm H_2O, respectively, during the second set of three breaths; and 40 cm H_2O and 20 cm H_2O, respectively, during the next six breaths. After performing the RM, the inspiratory pressure and PEEP were changed to the values observed immediately before starting the RM.

At the end of surgery, lung inflation was performed using an inspiratory pressure of 30 cm H_2O for 7 s in both the dependent and non-dependent lung in all three groups. Tracheal extubation was performed after neuromuscular recovery was confirmed. A chest X-ray was performed at 3 days after surgery.

Bronchoalveolar lavage (BAL) was performed via a fiberoptic bronchoscope in both the dependent and non-dependent lungs [8, 19, 20]. The end of the fiberoptic bronchoscope was positioned at the segmental bronchioles, and 50 mL of a sterile saline solution was administered and aspirated. The BAL was performed twice: first, during two-lung ventilation and before starting OLV, and second, immediately after the end of OLV. A 10 mL blood sample was obtained at the same time. The BAL samples were centrifuged at 200×*g* at 4 °C for 10 min. Blood samples were centrifuged at 1000×*g* at 4 °C for 15 min. The supernatants of the BAL samples and the separated plasma samples were stored at − 70 °C. Cytokines, including TNF-α, IL-1β, IL-6, IL-8, and IL-10, were analyzed via enzyme-linked immunosorbent assay using Procarta Cytokine Assay Kits (Affymetrix, Santa Clara, California).

Time under anesthesia, operation time, and the duration of OLV were recorded. The amount of propofol, remifentanil, and infused fluids administered during surgery were recorded. Hemodynamic data (including heart rate, mean arterial pressure, and cardiac index) and respiratory data (including TV, respiratory rate, PIP, plateau pressure, end-tidal CO_2, PaO_2/FiO_2 ratio, $PaCO_2$, and SaO_2) were recorded at the following time points: during two-lung ventilation and before the start of OLV (TLV), 30 min after the start of OLV (OLV-30), and at OLV-50, OLV-70, and 10 min after the end of OLV. The physiological dead space to V_T ratio was calculated using the following formula: $V_D/V_T = (PaCO_2 - EtCO_2)/PaCO_2$, where $EtCO_2$ is the end-tidal CO_2. The incidences of intraoperative events, such as PaO_2 level < 80 mmHg, SpO_2 level < 95%, PIP ≥ 30 cm H_2O, and plateau pressure ≥ 25 cm H_2O, were recorded, as well as the incidence of postoperative pulmonary and cardiovascular complications, such as pneumonia and atrial fibrillation, and abnormal findings on a postoperative chest X-ray, such as atelectasis, pulmonary edema, consolidation, and subcutaneous emphysema.

Statistical analysis

The primary outcome was the level of TNF-α in the BAL fluid of the dependent lung. TNF-α, a proinflammatory mediator produced by macrophages and monocytes, is detected in BAL fluids after mechanical ventilation [8, 20]. Secondary outcomes included the levels of IL-1β, IL-6, IL-8, and IL-10 in the BAL fluid of the dependent lung and TNF-α, IL-1β, IL-6, IL-8, and IL-10 in the serum and BAL fluid of the non-dependent lung. Sample size was calculated using an analysis of variance (ANOVA) based on the results of previous study [20]. It was estimated that a minimum of 60 patients would be required with an effect size of 0.47 when assuming a type 1 error of 0.05, a power of 0.8, and a drop-out rate of 20%. Sex, ASA physical status, preoperative pulmonary function test, lung pathology, operative region, and intraoperative and postoperative adverse events were compared using chi-squared or Fisher's exact tests. Weight, height, age, operation time, time under anesthesia, OLV duration, propofol and remifentanil amounts, infused fluids volumes, and preoperative respiratory data, such as PaO_2, $PaCO_2$, FEV_1, FVC, the FEV_1/FVC ratio, and carbon monoxide pulmonary diffusing capacity, were compared using ANOVA. Intraoperative hemodynamic and respiratory data, including heart rate, mean arterial pressure, cardiac index, TV, respiratory rate, PIP, plateau pressure, end-tidal CO_2, the PaO_2/FiO_2 ratio, and $PaCO_2$, SaO_2, and V_D/V_T levels, were compared using a linear mixed model (LMM). The levels of cytokines were logarithmically transformed to achieve homogenous variances of the data sets. If the concentration was below the detection limits of the assays, a value of 0.01 was entered [8]. LMM was used to analyze the cytokine data. Post hoc analyses were performed using Bonferroni's correction. SAS (version 9.2, SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. A P value < 0.05 denoted statistical significance.

Results

Sixty patients that successfully completed the study were included (Fig. 1). The patient characteristics are presented in Table 1. There were no significant differences in the results of preoperative pulmonary function tests, the length of operation time or time under anesthesia, OLV duration, infused fluid volume, or the dose of propofol or remifentanil among the three groups.

Cytokine levels are shown in Table 2. In the BAL fluids obtained from the dependent lung, TNF-α levels were higher after OLV in the PV than in the PVRM group ($P = 0.049$), whereas the levels of IL-1β, IL-6, IL-8, and IL-10 were not significantly different among the three groups. In the BAL fluid obtained from the non-dependent lung, none of the evaluated cytokines were significantly different among the groups. In serum samples, the level of IL-10 after OLV was higher in the traditional ventilation than in the PVRM group ($P = 0.027$), whereas the levels of IL-1β, IL-6, IL-8,

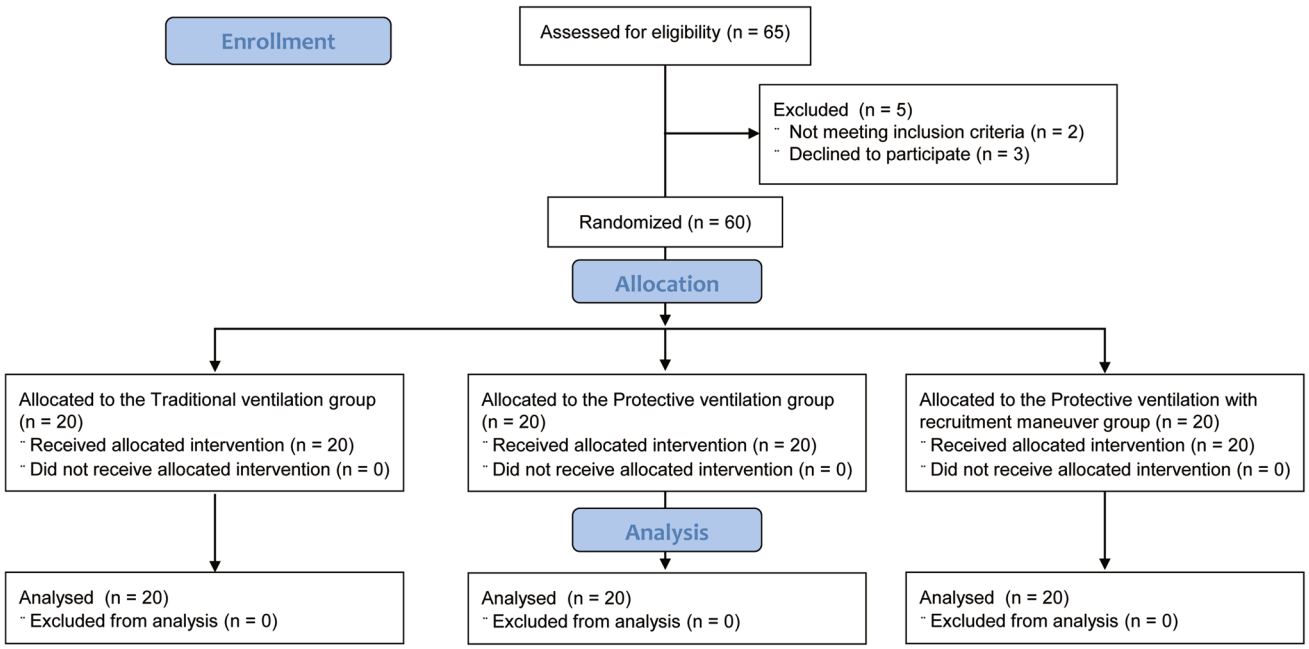

Fig. 1 Flow diagram of the study design

Table 1 Patient characteristics

	Traditional ventilation ($n=20$)	Protective ventilation ($n=20$)	Protective ventilation with recruitment maneuver ($n=20$)	*P* value
Age (years)	57 (32–74)	57 (31–76)	57 (40–77)	0.984
Sex, male/female	9/11	11/9	7/13	0.446
Height (cm)	162 ± 10	163 ± 8	160 ± 6	0.599
Weight (kg)	63 ± 9	64 ± 10	60 ± 6	0.288
ASA, 1/2	14/6	11/9	15/5	0.377
Smoking, former smoker/never smoker	4/16	6/14	4/16	0.799
Preoperative PaO_2 (mmHg)	99 ± 15	99 ± 16	99 ± 18	0.995
Preoperative $PaCO_2$ (mmHg)	44 ± 7	41 ± 5	42 ± 4	0.247
Preoperative FEV_1 (% of predicted)	109 ± 16	108 ± 14	108 ± 15	0.983
Preoperative FVC (% of predicted)	103 ± 13	102 ± 9	99 ± 14	0.627
Preoperative FEV_1/FVC ratio (% of predicted)	79 ± 6	77 ± 5	80 ± 8	0.336
Preoperative DLCO (% of predicted)	99 ± 20	99 ± 19	99 ± 16	> 0.999
Pulmonary function test, obstructive/restrictive/normal	1/1/18	1/0/19	1/1/18	0.053
Pathology, adenocarcinoma/NSCLC/BAC/Sqcc	16/1/3/0	15/2/2/1	17/2/1/0	0.920
Operative region, RUL/RML/RLL/LUL/LLL	8/2/0/4/6	4/2/7/5/2	5/3/7/3/2	0.070
Operation time (min)	159 ± 55	141 ± 36	141 ± 40	0.330
Anesthetic time (min)	206 ± 50	196 ± 43	196 ± 38	0.728
One-lung ventilation duration (min)	131 ± 40	121 ± 34	123 ± 38	0.665
Infused volume of lactated Ringer's solution (mL)	848 ± 344	748 ± 324	810 ± 353	0.649
Infused volume of 6% hydroxyethyl starch 130/0.4 (mL)	15 ± 67	20 ± 89	0	0.597
Propofol (mg)	1617 ± 643	1575 ± 525	1484 ± 235	0.691
Remifentanil (μg)	1356 ± 527	1247 ± 550	1406 ± 457	0.679

Data are presented as the mean (range), mean ± SD or the number of patients

ASA American Society of Anesthesiologists, *BAC* bronchioloalveolar carcinoma, *DLCO* carbon monoxide pulmonary diffusing capacity, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *LLL* left lower lobe, *LUL* left upper lobe, *NSCLC* non-small-cell lung carcinoma, *RLL* right lower lobe, *RML* right middle lobe, *RUL* right upper lobe, *Sqcc* squamous cell carcinoma

Table 2 Cytokine levels in the BAL obtained from the dependent and non-dependent lungs, and serum before/after OLV

	Traditional ventilation ($n=20$)	Protective ventilation ($n=20$)	Protective ventilation with recruitment maneuver ($n=20$)	*P* value		
				T vs. P	P vs. PR	T vs. PR
Dependent lung						
TNF-a (pg/mL)	0.90 (0.42–1.65)/1.16 (0.52–5.97)	0.72 (0.01–1.67)/0.99 (0.5–6.2)	0.82 (0.03–1.67)/0.57 (0.01–1.35)	> 0.999	0.049†	0.339
IL-1β (pg/mL)	0.61 (0.14–23.6)/1.07 (0.24–23.58)	0.9 (0.13–3.77)/0.77 (0.03–2.52)	1.29 (0.77–6.23)/0.29 (0.12–1.4)	0.897	0.966	0.135
IL-6 (pg/mL)	2.96 (0.11–8.75)/6.92 (0.32–26.08)	1.01 (0.01–5.78)/2.58 (0.12–10.32)	2.84 (0.01–7.89)/0.8 (0.01–7.78)	> 0.999	> 0.999	> 0.999
IL-8 (pg/mL)	43.62 (23.19–434.52)/90.61 (18.3–432.49)	31.55 (2.75–245.45)/28.89 (0.71–129.54)	93.18 (15.41–128.04)/50.53 (11.55–106.82)	0.867	> 0.999	> 0.999
IL-10 (pg/mL)	0.01 (0.01–0.11)/0.02 (0.01–0.33)	0.01 (0.01–0.03)/0.02 (0.01–0.32)	0.03 (0.01–0.07)/0.02 (0.01–0.18)	> 0.999	0.234	> 0.999
Non-dependent lung						
TNF-a (pg/mL)	0.86 (0.03–2.49)/6.97 (0.95–37.57)	0.05 (0.01–0.48)/1.07 (0.13–5.79)	0.6 (0.3–1.57)/8.93 (1.69–52.62)	> 0.999	> 0.999	> 0.999
IL-1β (pg/mL)	1.28 (0.29–2.61)/9.13 (1.42–38.27)	0.54 (0.03–2)/2.79 (0.72–6.24)	1.29 (0.19–6.16)/3.31 (1.96–12.75)	> 0.999	> 0.999	> 0.999
IL-6 (pg/mL)	3.02 (0.69–6.79)/99.56 (13.79–218.4)	2.26 (0.09–3.47)/6.11 (0.71–49.02)	2.57 (0.37–10.53)/48.39 (14.13–145.75)	0.835	0.400	> 0.999
IL-8 (pg/mL)	76.54 (45.36–210.41)/518.54 (179.31–831.79)	34.66 (9.37–158.41)/88.19 (15.52–260.99)	33.74 (19.86–108.27)/315.58 (99.37–801.91)	> 0.999	> 0.999	> 0.999
IL-10 (pg/mL)	0.02 (0.01–0.43)/0.04 (0.01–0.86)	0.01 (0.01–0.03)/0.02 (0.01–0.3)	0.02 (0.01–0.27)/0.31 (0.02–1.53)	> 0.999	0.363	0.284
Serum						
TNF-a (pg/mL)	0.01 (0.01–1.65)/0.38 (0.01–1.83)	0.01 (0.01–1.65)/0.01 (0.01–2.06)	0.21 (0.01–2.42)/0.01 (0.01–1.65)	> 0.999	0.599	0.743
IL-1β (pg/mL)	0.2 (0.01–0.63)/0.29 (0.01–0.97)	0.12 (0.01–0.52)/0.07 (0.01–0.61)	0.27 (0.01–0.58)/0.26 (0.01–0.5)	> 0.999	> 0.999	0.324
IL-6 (pg/mL)	0.21 (0.01–5.1)/22.22 (6.5–66.2)	0.01 (0.01–1.31)/8.13 (0.87–13.78)	0.01 (0.01–1.86)/10.09 (3.76–40.89)	> 0.999	> 0.999	> 0.999
IL-8 (pg/mL)	4.04 (0.01–5.58)/6.2 (3.61–9.99)	2.94 (0.01–5.29)/6.04 (0.01–7.88)	4.76 (0.01–6.63)/6.61 (2.17–7.42)	> 0.999	> 0.999	> 0.999
IL-10 (pg/mL)	0.45 (0.01–1.88)/1.35 (0.01–3.34)	0.12 (0.01–1.22)/0.18 (0.01–1.5)	0.38 (0.01–7.47)/0.57 (0.01–3.58)	0.195	> 0.999	0.027‡

The data are presented as the median (interquartile range)

BAL bronchoalveolar lavage, *P* protective ventilation, *PR* protective ventilation with recruitment maneuver, *T* traditional ventilation

†*P* value < 0.05: comparison between the protective ventilation and the protective ventilation with recruitment maneuver groups

‡*P* value < 0.05: comparison between the traditional ventilation and protective ventilation with recruitment maneuver groups

and TNF-α were not significantly different among the three groups.

The respiratory and hemodynamic data are shown in Table 3. TV was significantly lower during OLV in all groups. The decrease in TV was significantly smaller in the traditional ventilation than in the PV and PVRM groups. The decrease in the respiratory rate was significantly larger in the traditional ventilation than in the PV and PVRM groups. PIP and plateau pressure were significantly higher during OLV in all groups. The increases in the PIP and plateau pressure were significantly larger in the traditional ventilation than in the PV and PVRM groups. End-tidal CO_2 was not significantly different among the three groups. The PaO_2/FiO_2 ratio was significantly decreased during OLV in all groups. At 10 min after the end of OLV, the decrease in the PaO_2/FiO_2 ratio was significantly larger in the traditional ventilation than in the PV group. There was no significant difference in the $PaCO_2$ level among the three groups, although it was significantly higher at certain time points in all groups. There was no significant difference in the level of SaO_2 among the three groups, although it was significantly lower at certain time points during OLV in the PV group. There was no significant difference in $V_{D/}V_T$ among three groups, although it was significantly higher at certain time points during OLV in the PV group. Hemodynamic data,

Table 3 Respiratory and hemodynamic data

	TLV	OLV 30	OLV 50	OLV 70	OLV end
Tidal volume (mL)					
Traditional ventilation	549 ± 104	483 ± 114†‡*	480 ± 121†‡	493 ± 127†‡*	503 ± 91†
Protective ventilation	450 ± 71	322 ± 62†	324 ± 56†	326 ± 51†	421 ± 71
Protective ventilation with recruitment maneuver	420 ± 51	313 ± 35†	308 ± 39†	305 ± 41†	405 ± 65
Respiratory rate (breaths/min)					
Traditional ventilation	12 ± 2	10 ± 2	10 ± 3‡*	11 ± 2‡*	10 ± 2
Protective ventilation	13 ± 2	13 ± 3	14 ± 2	15 ± 2	13 ± 1
Protective ventilation with recruitment maneuver	14 ± 2	14 ± 2	14 ± 2	15 ± 2	13 ± 2
Peak inspiratory pressure (cm H_2O)					
Traditional ventilation	17 ± 2	26 ± 2†‡*	26 ± 2†‡*	25 ± 2†*	19 ± 5
Protective ventilation	18 ± 3	22 ± 4†	23 ± 4†	24 ± 4†	21 ± 4†
Protective ventilation with recruitment maneuver	18 ± 3	22 ± 4†	23 ± 4†	22 ± 3†	20 ± 3
Plateau pressure (cm H_2O)					
Traditional ventilation	17 ± 2	23 ± 3†‡*	23 ± 3†‡*	23 ± 3†*	18 ± 5
Protective ventilation	17 ± 3	20 ± 3†	21 ± 4†	21 ± 4†	19 ± 4
Protective ventilation with recruitment maneuver	17 ± 2	20 ± 4†	21 ± 4†	20 ± 4†	19 ± 4
End-tidal CO_2 (mmHg)					
Traditional ventilation	31 ± 3	32 ± 3	32 ± 4	32 ± 3	30 ± 4
Protective ventilation	33 ± 4	36 ± 5	35 ± 4	36 ± 4	34 ± 5
Protective ventilation with recruitment maneuver	33 ± 3	35 ± 2	35 ± 3	35 ± 3	34 ± 3
PaO_2/FiO_2 ratio					
Traditional ventilation	425 ± 133	170 ± 54†	198 ± 63†	241 ± 82†	341 ± 105‡
Protective ventilation	442 ± 156	150 ± 58†	193 ± 89†	209 ± 100†	454 ± 123
Protective ventilation with recruitment maneuver	475 ± 151	202 ± 91†	218 ± 102†	241 ± 121†	428 ± 122
$PaCO_2$ (mmHg)					
Traditional ventilation	38 ± 4	43 ± 5†	41 ± 7	40 ± 4	41 ± 4
Protective ventilation	40 ± 4	49 ± 7†	47 ± 6†	47 ± 5†	45 ± 5†
Protective ventilation with recruitment maneuver	42 ± 5	48 ± 6†	47 ± 4†	46 ± 5	46 ± 6
SaO_2 (mmHg)					
Traditional ventilation	100 ± 1	99 ± 2	99 ± 1	99 ± 2	99 ± 1
Protective ventilation	100 ± 1	98 ± 2†	98 ± 6	99 ± 2†	100 ± 1
Protective ventilation with recruitment maneuver	100 ± 1	99 ± 2	99 ± 2	99 ± 1	100 ± 1
V_D/V_T (%)					
Traditional ventilation	19 ± 7	25 ± 6	24 ± 10	21 ± 6	25 ± 8
Protective ventilation	18 ± 8	27 ± 5†	26 ± 5	23 ± 5	23 ± 8
Protective ventilation with recruitment maneuver	21 ± 9	27 ± 5	25 ± 6	24 ± 5	25 ± 7
Heart rate (beats/min)					
Traditional ventilation	66 ± 10	69 ± 11	65 ± 8	65 ± 10	71 ± 13
Protective ventilation	67 ± 12	71 ± 9	70 ± 11	68 ± 11	69 ± 11
Protective ventilation with recruitment maneuver	62 ± 7	68 ± 9	65 ± 10	67 ± 9	65 ± 8
Mean arterial pressure (mmHg)					
Traditional ventilation	77 ± 14	79 ± 10	82 ± 10	87 ± 13†	82 ± 10
Protective ventilation	79 ± 20	78 ± 10	84 ± 12	96 ± 12	88 ± 14
Protective ventilation with recruitment maneuver	77 ± 11	80 ± 10	81 ± 11	83 ± 10	88 ± 10†
Cardiac index (L/min/m^2)					
Traditional ventilation	3 ± 1	3 ± 1	3 ± 1	3 ± 1	3 ± 1
Protective ventilation	3 ± 1	3 ± 1	3 ± 1	3 ± 1	3 ± 1
Protective ventilation with recruitment maneuver	3 ± 1	3 ± 1	3 ± 1	3 ± 1	3 ± 1

The data are presented as the mean ± SD

OLV one-lung ventilation, *TLV* during two-lung ventilation and before the start of OLV, *OLV 30* at 30 min after the start of OLV, *OLV 50* at 50 min after the start of OLV, *OLV 70* at 70 min after the start of OLV, *OLV end* at 10 min after the end of OLV

†*P* value < 0.05: compared to the TLV value within the group

‡*P* value < 0.05: compared to the protective ventilation group

Table 3 (continued)

*P value < 0.05: compared to the protective ventilation with recruitment maneuver group

including heart rate, mean arterial pressure, and cardiac index were similar among the three groups.

Intraoperative and postoperative complications are shown in Table 4. There were no significant differences among the three groups in this category except that the risk of experiencing an intraoperative PIP more than 30 cm H_2O was higher in the traditional ventilation than in the PVRM group ($P = 0.024$). Intraoperative hypoxia (indicated as a PaO_2 level < 80 mmHg) was observed in 12% of patients and the lowest observed PaO_2 level was 72 ± 5 mmHg.

Discussion

RMs performed before OLV enhanced aeration and reduced cyclic recruitment during OLV in a pig experimental model [21]. A previous retrospective study demonstrated that combining a small TV with PEEP without an RM was linked to an increased risk of 30-day mortality in patients undergoing general anesthesia [12]. We therefore speculated that the RM may be critical in lung-protective ventilatory strategy.

In our study, after OLV, the level of TNF-α in the BAL of the dependent lung was significantly higher in the PV than in the PVRM group. Alveolar macrophages and monocytes, which produce TNF-a, are recruited into the alveolar space following injury to the alveolocapillary units and have been detected in BAL fluids after mechanical ventilation [19, 20]. Therefore, the low level of TNF-α in the ventilated-dependent lung indicates that PVRM may improve alveolar damage-induced inflammation after OLV. We found no inflammatory response differences in the ventilated lung between the traditional ventilation and PV groups; in line with previous reports that showed no significant difference in pulmonary cytokine levels between patients treated with a large 12–15 mL/kg TV without PEEP and those treated with a small 6 mL/kg TV with 10 cm H_2O PEEP during thoracotomy [10]. However, in another report, IL-8 and TNF-α levels were significantly higher after OLV in the BAL of the dependent lung, and this increase was significantly smaller when a small 5 mL/kg TV was applied without PEEP than when a large 10 mL/kg TV was applied without PEEP in open thoracic surgery [8]. This variation in BAL cytokine concentrations may result from differences in the type and extent of surgical trauma and the ventilatory strategy. We found no significant differences in BAL cytokine level increases in the non-dependent lung. The primary cause of inflammation in the non-dependent lung was surgical injury [22]; therefore, the inflammatory response may not depend on ventilatory strategy.

In our study, serum cytokine IL-10 levels were higher after OLV in the traditional ventilation than in the PVRM group. IL-10 is an immunoregulatory cytokine that reduces the severity of lung injury by counteracting the expression of proinflammatory cytokines, which increases in the serum after OLV [23]. Our finding is consistent with the results described in previous reports in which the RM, when combined with PV, resulted in significantly lower levels of IL-8 and IL-10 being released into the serum after cardiopulmonary bypass in patients who underwent cardiac surgery [24]. Therefore, based on our study results, PVRM may result in better systemic inflammatory responses. Although we did not observe a significant difference in IL-6 plasma

Table 4 Intraoperative events and postoperative complications

	Traditional ventilation ($n = 20$)	Protective ventilation ($n = 20$)	Protective ventilation with recruitment maneuver ($n = 20$)	P value
Intraoperative PaO_2 < 80 mmHg	1	4	2	0.478
Intraoperative SpO_2 < 95%	0	1	0	> 0.999
Intraoperative peak inspiratory pressure more than 30 cm H_2O	11†	6	3	0.034
Intraoperative plateau pressure more than 25 cm H_2O	7	4	4	0.602
Occurrence of postoperative complications	3	1	2	0.863
Abnormal finding on chest X-ray				
Atelectasis	9	8	6	0.713
Pulmonary edema	0	1	1	> 0.999
Consolidation	2	4	2	0.710
Subcutaneous emphysema	1	0	3	0.310

The data are presented as the number of patients

†P value < 0.05: comparison between the traditional ventilation and protective ventilation with recruitment maneuver groups

levels, serum IL-6 has been reported to increase less with PV than with traditional ventilation in patients undergoing esophagectomy [11]. Serum cytokine levels may not specifically reflect the influence of the ventilation method on systemic inflammation due to concurrent surgical injury [25]. PVRM may result in a better systemic inflammatory response, although the contributing mechanism remains unclear.

A longer OLV duration was associated with a proportionally higher degree of inflammation [2, 26]. Moreover, an inflammatory response may worsen because of radical oxygen species production and absorption atelectasis development with a high FiO_2 concentration [27]. We found no differences in OLV duration, and FiO_2 level was adjusted according to oxygen saturation and PaO_2 regardless of the group. The intraoperative total volume of administered fluid critically contributes to the occurrence of postoperative complications [6]. We therefore administered the same types of crystalloids while monitoring the cardiac index, and we found that there was no significant difference in the fluid amount across the groups. A previous study demonstrated that video-assisted thoracic surgery provoked a smaller cytokine response than conventional open surgery due to the reduced extent of the operation [22]. We therefore applied the same surgical method regardless of group assignment to eliminate surgical bias. There are several limitations to our study. First, previous reports have suggested the use of the bronchoscopic microsampling method to obtain epithelial lining fluid from small airways [28]; cytokine levels may have differed had we chosen to use this method instead of BAL. Second, the incidence of postoperative pulmonary and cardiovascular complications was not significantly different among the groups, but there was a significant difference in the pulmonary inflammatory response. This may be because the sample size calculation for this study was based on cytokine levels and not postoperative outcomes, making the sample size relatively small. Therefore, the clinical impact on the postoperative course of the attenuated pulmonary inflammation remains to be determined and a larger-scale study is needed to more precisely identify differences in postoperative complications and mortality.

In conclusion, we found that PVRM resulted in less local inflammation in the ventilated lung than was observed with PV alone and less systemic inflammation than was observed with traditional ventilation. We therefore suggest that the application of an RM may be needed when using PV to effectively reduce the inflammatory response in the ventilated lung during video-assisted thoracoscopic lobectomy. However, larger multi-center clinical trials should be performed to confirm the effect of PVRM on clinical outcomes.

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Compliance with ethical standards

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