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Protective Ventilation Influences Systemic Inflammation after Esophagectomy

A Randomized Controlled Study

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Background: **Esophagectomy induces a systemic inflammatory response whose extent has been recognized as a predictive factor of postoperative respiratory morbidity. The aim of this study was to determine the effectiveness of a protective ventilatory strategy to reduce systemic inflammation in patients undergoing esophagectomy.**

Methods: **The authors prospectively investigated 52 patients undergoing planned esophagectomy for cancer. Patients were randomly assigned to a conventional ventilation strategy (n = 26; tidal volume of 9 ml/kg during two-lung and one-lung ventilation; no positive end-expiratory pressure) or a protective ventilation strategy (n = 26; tidal volume of 9 ml/kg during two-lung ventilation, reduced to 5 ml/kg during one-lung ventilation; positive end-expiratory pressure 5 cm H_2O throughout the operative time).**

Results: **Plasmatic levels of interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor α were measured perioperatively and postoperatively. Pulmonary function and postoperative evolution were also evaluated. Patients who received protective strategy had lower blood levels of IL-1β, IL-6, and IL-8 at the end of one-lung ventilation (0.24 [0.15–0.40] *vs.* 0.56 [0.38–0.89] pg/ml, $P < 0.001$; 91 [61–117] *vs.* 189 [127–294] pg/ml, $P < 0.001$; and 30 [22–45] *vs.* 49 [29–69] pg/ml, $P < 0.05$, respectively) and 18 h postoperatively (0.18 [0.13–0.30] *vs.* 0.43 [0.34–0.54] pg/ml, $P < 0.001$; 54 [36–89] *vs.* 116 [78–208] pg/ml, $P < 0.001$; 16 [11–24] *vs.* 35 [28–53] pg/ml, $P < 0.001$, respectively). Protective strategy resulted in higher oxygen partial pressure to inspired oxygen fraction ratio during one-lung ventilation and 1 h postoperatively and in a reduction of postoperative mechanical ventilation duration (115 ± 38 *vs.* 171 ± 57 min, $P < 0.001$).**

Conclusion: **A protective ventilatory strategy decreases the proinflammatory systemic response after esophagectomy, improves lung function, and results in earlier extubation.**

ESOPHAGECTOMY is a major surgical procedure requiring a prolonged period of one-lung ventilation (OLV). This procedure is marked by an important inflammatory response[1–3]; the extent of this response and the occurrence of perioperative hypoxemia have been recognized as predictive factors of postoperative respiratory morbidity.[4,5]

In patients with acute respiratory distress syndrome, mechanical ventilation with low tidal volume (V_T) and positive end-expiratory pressure (PEEP) has been shown to reduce pulmonary and systemic cytokine release and to improve gas exchange and outcome.[6–8] In patients with normal lungs, two studies have suggested that applying PEEP and reducing V_T did not influence plasma cytokine release during mechanical ventilation for elective surgery.[9,10] However, animal studies have reported that conventional mechanical ventilation may activate cytokine response even without preexisting lung injury[11] and that it may induce the development of further lung injury when applied after lipopolysaccharide injection.[12] Moreover, it seems that, during OLV, V_T is frequently maintained at the same level as during two-lung ventilation without PEEP.[13,14] This maintenance corresponds to a high-volume ventilation with potentially deleterious effects even for a period of less than 90 min.[5,15] Recent experimental data have demonstrated a potential reduction of such phenomenon by using reduced V_T and PEEP.[15] Therefore, the benefits of a protective ventilatory strategy in a selected population of patients without preexisting lung disease and undergoing a major thoracic–abdominal surgery such as esophagectomy could be enhanced.

The aim of this prospective, randomized study was to determine whether a ventilatory strategy based on the reduction of V_T during OLV and a moderate level of PEEP could reduce the systemic proinflammatory cytokine response associated with esophagectomy. Its impact on oxygenation, extravascular lung water amount, and duration of postoperative mechanical ventilation was also evaluated.

Materials and Methods

Study Population

The protocol was approved by the ethics committee of the hospital (comité consultatif de protection des biens et des personnes en recherche biomédicale de Marseille 1, France), and informed consent was obtained from each patient. Eligible patients met the following criteria: (1) age 18 yr or older, (2) planned esophagectomy for esophageal cancer, and (3) acceptance of postoperative thoracic epidural analgesia. Exclusion criteria included New York Heart Association class III or IV, preexisting chronic obstructive pulmonary disease with forced expiratory volume in 1 s of

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less than 80% of predicted and/or forced expiratory volume in 1 s over forced vital capacity ratio of less than 0.7,[16] chronic renal failure (serum creatinine > 200 μM), altered liver function (Child-Pugh class B or more), preoperative corticosteroid treatment during the month before inclusion or a preoperative acute infection suspected because of a temperature greater than 38°C or less than 36°C, leukocyte count greater than 10×10^9 or less than 4×10^9, or any new pulmonary infiltrate on the systematic chest radiograph.

Patient Treatment

Anesthetic and surgical management were standardized for each patient. Anesthesia was induced and maintained with propofol, sufentanil, and cisatracurium. After tracheal intubation with a double-lumen tube (Mallinckrodt, Athlone, Ireland), under fiberoptic bronchoscopy, mechanical ventilation was initiated (Julian®; Dräger, Lübeck, Germany) and the respiratory rate was adjusted to keep arterial blood carbon dioxide partial pressure ($Paco_2$) between 35 and 45 mmHg throughout anesthesia. The initial inspired oxygen fraction (Fio_2) was 0.5 using oxygen-and-air mixture and was increased if necessary to keep a transcutaneous saturation greater than 90%. A warming blanket system and fluid warmers were used to prevent hypothermia during surgery. Standardized fluid replacement consisted of 10 ml/kg ideal body weight lactated Ringer's solution (RL; B. Braun, Melsungen, Germany) preoperatively, followed by 10 ml $\cdot kg^{-1} \cdot h^{-1}$ perioperatively. If mean arterial pressure was lower than 70 mmHg for more than 5 min, an additional fluid challenge was achieved with 10 ml/kg hydroxyethyl starch (Voluven®; Fresenius Kabi, Bad Homburg, Germany) eventually repeated once.

The same experienced surgeons (C.D., P.T.; 25–30 transthoracic esophagectomies per year) both conducted each operation and were blinded to the strategy used.[17] Surgical procedures included, first, a median laparotomy with confection of a neoesophagus using the stomach and, second, a right thoracotomy with right pulmonary exclusion in lateral decubitus allowing subtotal esophagectomy combined with two fields lymphadenectomy and esophageal reconstruction through the thoracic route.[18]

After surgery, all patients were transferred to an intensive care unit. Extubation was performed when patients met the following extubation criteria: (1) temperature greater than 36°C, (2) mean arterial pressure greater than 70 mmHg, (3) arterial oxygen partial pressure (Pao_2)/Fio_2 ratio greater than 200 mmHg with hemoglobin level greater than 8 g/dl, (4) ratio of respiratory frequency to V_T less than 105 breaths $\cdot min^{-1} \cdot l^{-1}$ under 10 cm H_2O pressure support and 5 cm H_2O PEEP, and (5) adequate cough during suctioning. Patients were cared for by attending physicians not involved in the protocol and blinded to the allocated group.

Study Protocol

Before anesthetic induction, patients were randomly assigned by a concealed allocation approach using opaque sealed envelopes containing the randomization schedule. Randomization was realized by computer-generated codes maintained in sequentially numbered, opaque envelopes that were opened before induction of general anesthesia. Patients received either a conventional ventilation (CV) or a protective ventilation (PV) strategy. The CV strategy used a V_T of 9 ml/kg predicted body weight and no PEEP throughout the intervention (*i.e.*, during two-lung and one-lung ventilation). The PV strategy used a V_T of 9 ml/kg during the two-lung ventilation with a reduction to 5 ml/kg during OLV associated with 5 cm H_2O PEEP throughout the operative time (*i.e.*, during two-lung and one-lung ventilation). PEEP was removed for the transfer in the intensive care unit and was only applied again in both groups after the patient was under pressure support before extubation. The predicted body weight of male patients was calculated as equal to 50 + 0.91 (centimeters of height-152.4), that of female patients was calculated as equal to 45.5 + 0.91 (centimeters of height-152.4).[8] In both strategies, neither continuous positive airway pressure on the excluded lung nor recruitment maneuver was used. In case of perioperative hypoxemia, the only treatment used was an increase in Fio_2. The anesthesiologists were not blinded to the strategy used, but they were not implicated in the collection of the data.

Six sets of measurements were successively obtained: $T_{Baseline}$, baseline time after anesthetic induction, hemodynamic and respiratory stabilization, and before ventilatory strategy application; T_{Abdo}, at the end of abdominal time; $T_{OLV\ 15}$ and $T_{OLV\ End}$, 15 min after initiation and at the end of OLV, respectively; $T_{Postop\ 1}$ and $T_{Postop\ 18}$, 1 and 18 h after the end of the surgical procedure, respectively.

Measurements

According to the extensive use of interleukin (IL)-6 as a marker both of surgical-induced injury and of ventilator-induced lung injury,[1,19–21] the primary endpoint was the change of IL-6 level related to the ventilatory strategy used. To confirm the changes observed with IL-6, several others cytokines (tumor necrosis factor α [TNF- α], IL-1β, and IL-8) implicated in the proinflammatory response after esophagectomy were also studied. Arterial blood samples for measurement of serum TNF-α, IL-1β, IL-6, and IL-8 were collected at $T_{Baseline}$, T_{Abdo}, $T_{OLV\ End}$, and $T_{Postop\ 18}$. Samples were collected into nonpyrogenic, sterile falcon tubes. Serum was separated by cold centrifugation of the blood at 1,500*g* for 10 min and stored at −70°C. To improve the homogeneity of measurements, all of the samples were analyzed at the same time with the same assay reagents by the same laboratory technician blinded to the strategy used. Serum TNF-α, IL-1β, IL-6, and IL-8 were measured using enzyme-linked immunosorbent assay (human TNF-α, IL-1β,

IL-8 Immunoassay Quantikine [R&D Systems, Inc., Minneapolis, MN] and IL-6 enzyme-linked immunosorbent assay [Immunotech, Beckman-Coulter, Villepinte, France]). The lower detection limits for these kits are 5, 0.1, 10, and 6 pg/ml, respectively.

Secondary endpoints included the Pa_{O_2}/F_{IO_2} ratio, the amount of extravascular lung water indexed to the body weight (EVLWI), and the ratio of EVLWI to intrathoracic blood volume indexed to body weight as an indicator of pulmonary permeability.[22] At $T_{Baseline}$, $T_{Postop\ 1}$, and $T_{Postop\ 18}$, the transpulmonary double-indicator dilution method was used to measure cardiac index, intrathoracic blood volume indexed to body weight, and EVLWI as described previously.[23] Dilution curves for 25 mg indocyanine green (Infracyanine®; SERB, Paris, France) dissolved in 12.5 ml iced 5% glucose were recorded in the descending aorta using a thermistor-tipped fiberoptic arterial catheter (Pulsiocath PV2024-4F; Pulsion Medical Systems, Munich, Germany) advanced *via* the femoral artery. Cardiac index and volumes were determined by a computer (COLD-Z-021; Pulsion Medical Systems, Munich, Germany). An average was calculated from three measurements performed at random moments during the ventilatory cycle.

Power and Statistical Analysis

Data were analyzed using the SPSS 12.0 package (SPSS Inc., Chicago, IL). Based on previous data,[24,25] the calculated sample size was 24 subjects per group to detect a difference in mean IL-6 concentration of 50%, an estimated SD of 60%, with a power of 80% and a 5% risk of type I error. Results are expressed as mean ± SD or median [interquartile range] for quantitative variables and as percentage for qualitative variables. The Student *t* test or Mann–Whitney U test was used for quantitative variables. The Pearson chi-square or Fisher exact test was applied for qualitative variables. Two-way repeated-measures analysis of variance followed by a Tukey *post hoc* test was used to evaluate the effects of time, ventilation strategy, and interaction. Cytokine levels were compared after $\log_{10}$ transformation. $P < 0.05$ was considered statistically significant.

Results

Patients

From September 2002 to December 2004, patients were consecutively recruited from the thoracic surgical unit of the University Hospital of Sainte Marguerite, Marseille, France. Of the 55 eligible patients, 52 were randomized and, according to an intention-to-treat analysis, were finally analyzed (fig. 1). Demographic and intraoperative characteristics did not differ between groups (tables 1 and 2). Among the patients studied, there was no patient treated with drugs potentially affecting cyto-

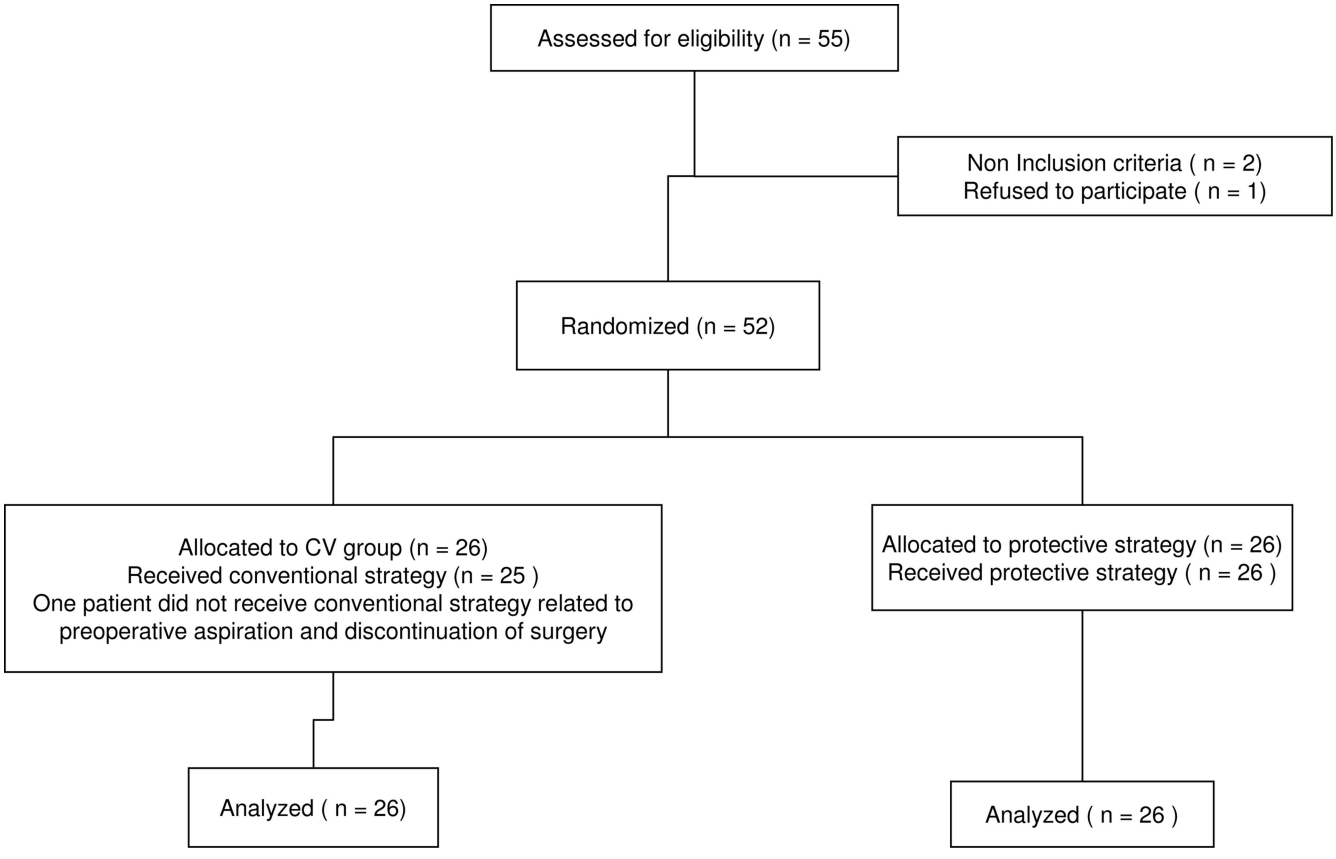

Fig. 1. Flow diagram of subjects. CV = conventional ventilation.

Table 1. Characteristics of the Patients at Study Inclusion before Randomization

	Conventional Ventilation (n = 26)	Protective Ventilation (n = 26)	*P* Value
Age, yr	60 ± 8.5	61 ± 10	0.69
Sex, M/F	22/4	21/5	0.99
Body mass index, kg/m^2	24 ± 3.5	24 ± 4	0.99
ASA physical status, n (%)			
I	6 (24)	6 (24)	
II	17 (65)	16 (61)	0.92
III	3 (11)	4 (15)	
NYHA, n (%)			
I	13 (50)	10 (38)	
II	10 (38)	15 (58)	0.30
III	3 (11)	1 (4)	
Weight loss, kg	3.5 ± 4.5	4 ± 6	0.74
Previous chemotherapy–radiation therapy	10 (46%)	11 (42%)	0.99
Smoking history, n (pack/yr)	18 (32 ± 24)	20 (37 ± 20)	0.75
FEV_1, % predicted	96 ± 18	93 ± 19	0.56
FVC, % predicted	99 ± 13	98 ± 14	0.79
Pa_{O_2}, % predicted	94 ± 12	93 ± 13	0.77
Tumour histology, n (%)			
Adenocarcinoma	15 (56)	16 (60)	0.99
Squamous cell	11 (44)	10 (40)	
Stage pTNM (UICC), n (%)			
I	7 (28)	7 (28)	
IIA	7 (24)	5 (20)	0.77
IIB	3 (12)	6 (20)	
III	9 (36)	8 (32)	

Data are expressed as mean ± SD unless otherwise noted.

ASA= American Society of Anesthesiologists; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; NYHA = New York Heart Association; Pa_{O_2} = partial pressure of oxygen.

kine kinetics and action (antiinflammatory drugs, corticosteroids).

Cytokine Blood Levels

A marked inflammatory response occurred during and after esophagectomy. Indeed, analysis of variance revealed an increase over time in blood levels of all cytokines (fig. 2) except TNF-α, which remained below the detection level of 5 pg/ml throughout the study (data not shown). Concentrations of IL-1β, IL-6, and IL-8 were significantly higher at T_{Abdo}, $T_{OLV\ End}$, and $T_{Postop\ 18}$ as compared with $T_{Baseline}$. The PV strategy resulted in less systemic inflammation from the end of OLV to the postoperative period compared with the CV strategy. Indeed IL-1β, IL-6, and IL-8 levels were lower in the PV group at $T_{OLV\ End}$ (0.24 [0.15–0.40] *vs.* 0.56 [0.38–0.89] pg/ml, $P < 0.001$; 91 [61–117] *vs.* 189 [127–294] pg/ml, $P < 0.001$; and 30 [22–45] *vs.* 49 [29–69] pg/ml, $P < 0.05$, respectively) and at $T_{Postop\ 18}$ (0.18 [0.13–0.30] *vs.* 0.43 [0.34–0.54] pg/ml, $P < 0.001$; 54 [36–89] *vs.* 116 [78–208] pg/ml, $P < 0.001$; and 16 [11–24] *vs.* 35 [28–53] pg/ml, $P < 0.001$, respectively) (fig. 2).

Pulmonary and Hemodynamic Variables

The PV strategy resulted in better oxygenation preservation. Indeed, whereas Pa_{O_2}/Fi_{O_2} ratio significantly decreased over time and was the lowest during OLV, it was higher in the PV group from $T_{OLV\ 15}$ to $T_{Postop\ 1}$ (fig. 3). Pa_{CO_2} increased in both groups from T_{Abdo} to $T_{OLV\ End}$ as compared with baseline values and was higher in the PV group at $T_{OLV\ 15}$ and $T_{OLV\ End}$ despite an increase in respiratory rate (table 3). Similarly, plateau airway pres-

Table 2. Intraoperative Data of the Patients

	Conventional Ventilation (n = 25)	Protective Ventilation (n = 26)	*P* Value
Surgery duration, min	295 ± 54	309 ± 71	0.43
One-lung ventilation duration, min	89 ± 29	85 ± 29	0.59
Perioperative mechanical ventilation duration, min	591 ± 94	574 ± 82	0.49
Perioperative blood loss, ml	629 ± 301	664 ± 325	0.68
Perioperative urine output, ml	1,031 ± 615	1,021 ± 519	0.95
Perioperative fluid administration, l	7.8 ± 1.9	7.8 ± 2.1	0.99
Perioperative transfusions, events	4 (15%)	6 (23%)	0.72
Perioperative transfusions, units	0.3 ± 0.7	0.5 ± 0.9	0.37

Data are expressed as mean ± SD unless otherwise noted.

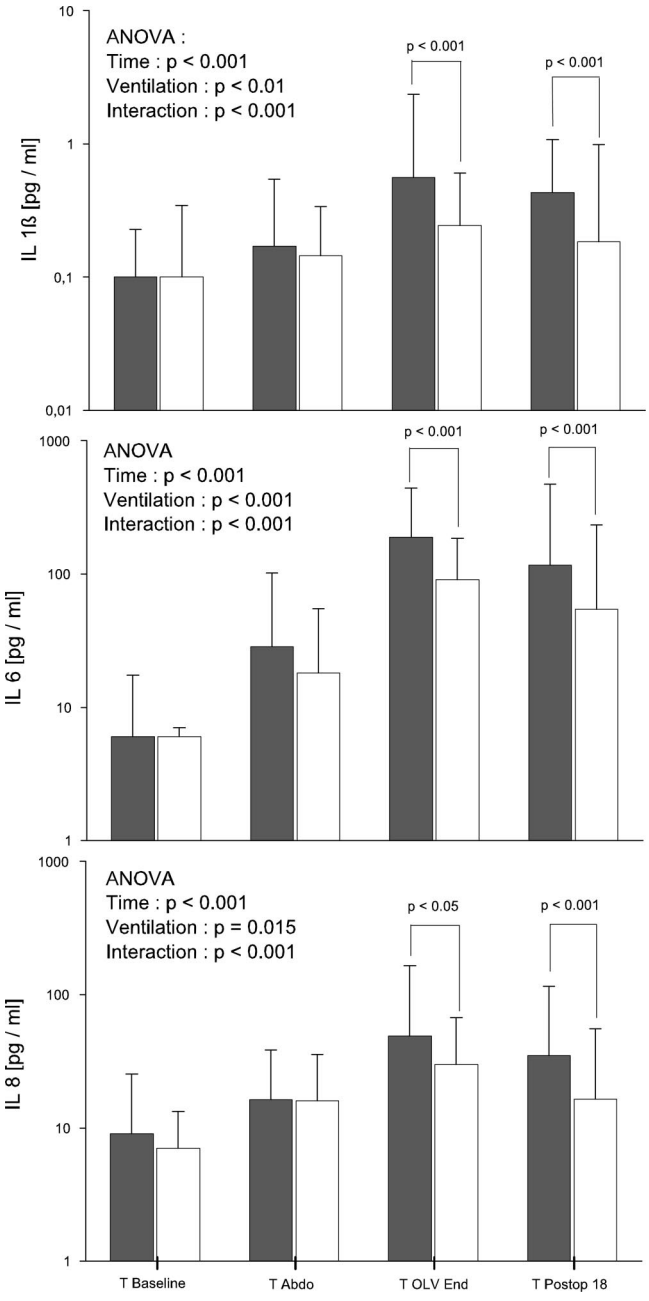

Fig. 2. Time course of blood cytokine levels in conventional ventilation group (*gray bars*) and protective ventilation group (*white bars*) at baseline ($T_{Baseline}$), at the end of abdominal time (T_{Abdo}), at the end of one-lung ventilation time ($T_{OLV\ End}$), and 18 h postoperatively ($T_{Postop\ 18}$). Data are expressed as median and 90th percentile. ANOVA = analysis of variance; IL = interleukin.

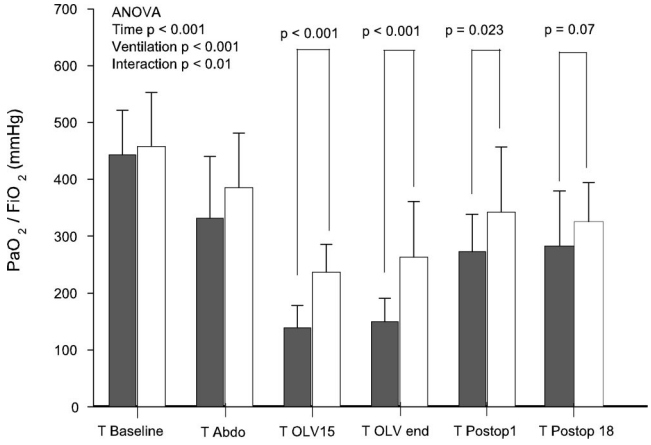

Fig. 3. Time course of arterial oxygen partial pressure/inspired oxygen fraction ratio (Pao_2/Fio_2) in conventional ventilation group (*gray bars*) and protective ventilation group (*white bars*) at baseline ($T_{Baseline}$), at the end of abdominal time (T_{Abdo}), after 15 min of one-lung ventilation ($T_{OLV\ 15}$), at the end of one-lung ventilation time ($T_{OLV\ End}$), and 1 h postoperatively ($T_{Postop\ 1}$). Data are expressed as mean and SD. ANOVA = analysis of variance. $T_{Postop\ 18}$ = 18 h postoperatively.

sure increased from $T_{OLV\ 15}$ to $T_{Postop\ 1}$ but was lower in the PV group during the OLV period (table 3). Heart rate and cardiac index increased with time in both groups from $T_{OLV\ End}$ to $T_{Postop\ 18}$ regardless of the ventilatory strategy (table 3). Use of the PV strategy also prevented the increase in EVLWI amount. The EVLWI amount and EVLWI/indexed intrathoracic blood volume ratio significantly increased at $T_{Postop\ 1}$ in the CV group and were higher than in the PV group (fig. 4). In addition, EVLWI remained higher than baseline values at $T_{Postop\ 18}$ in the CV group. There was no difference in type of fluid administered during the study protocol.

Postoperative Outcome

The duration of postoperative mechanical ventilation from intensive care unit admission to extubation was shorter in the PV group (table 4). However, there was no difference between the two groups with regard to postoperative morbidity, intensive care duration of stay, or number of days alive discharged from the hospital at day 30 (table 4).

Discussion

This study has shown that the reduction of V_T during OLV and the use of a PEEP of 5 cm H_2O during the overall ventilation period reduced the systemic proinflammatory response after esophagectomy. Better oxygenation and a shorter duration of postoperative ventilation were accomplished. Moreover, the use of this PV strategy was associated with a lower EVLWI increase.

The current study is the first to demonstrate that perioperative mechanical ventilation *per se* is an important factor in preventing part of the alterations in lung function and reducing the increase in plasmatic cytokine response in surgical patients without previous lung disease. Several studies have evaluated the impact of ventilatory strategies on inflammatory response and pulmonary function during major surgery.[9,10,26] In contrast to our findings, their results indicated that mechanical ventilation with high V_T and no PEEP did not result in higher cytokine levels when compared with strategies including a reduction of V_T associated with PEEP during major

Table 3. Respiratory and Hemodynamic Variables

	$T_{Baseline}$		T_{Abdo}		$T_{OLV\ 15}$		$T_{OLV\ End}$	
	CV	PV	CV	PV	CV	PV	CV	PV
RR, V_T/min	12 ± 1	12 ± 1	12 ± 2	13 ± 2	12 ± 2	15 ± 3*†	12 ± 2	15 ± 3*†
V_T, ml	565 ± 54	551 ± 77	561 ± 56	547 ± 64	563 ± 50	340 ± 41*†	560 ± 58	342 ± 38*†
Pplat, cm H_2O	14 ± 3	14.5 ± 2	16 ± 3	16 ± 3	28 ± 3†	21 ± 3.5†‡	26 ± 3†	20 ± 3.5†‡
Arterial pH	7.42 ± 0.04	7.41 ± 0.05	7.37 ± 0.03§	7.35 ± 0.08§	7.36 ± 0.1§	7.32 ± 0.04§*	7.36 ± 0.05§	7.29 ± 0.07§*
$Paco_2$, mmHg	39 ± 6	39 ± 4	43 ± 4†	45 ± 6†	42 ± 4†	48 ± 9*†	43 ± 5†	49 ± 6*†
MAP, mmHg	80 ± 11	74 ± 12	78 ± 10	81 ± 11	79 ± 11	75 ± 13	79 ± 13	78 ± 13
HR, beats/min	63 ± 14	62 ± 13	71 ± 14	68 ± 12	76 ± 13†	76 ± 14†	84 ± 15†	77 ± 17†
CI, $l \cdot min^{-1} \cdot kg^{-1}$	2.6 ± 0.7	2.7 ± 1.0	—	—	—	—	3.3 ± 1.0†	3.2 ± 1.1†

surgical procedures.[10] Nevertheless, the inflammatory response was studied in a nonhomogenic group of surgical procedures, and OLV was seldom used.[9,10,26] In contrast, our work has focused on one uniform surgical procedure performed by the same trained surgical team, which reinforced the comparability of groups.[27] Moreover, esophagectomy required left OLV, which, although limited in time, has been reported to promote ventilation-induced lung injury in both experimental and clinical settings with similar duration.[5,15] Although the exclusion of one lung and the use of OLV should theoretically include a reduction of V_T to 5 ml/kg, the hypothetic risk of derecruitment and hypoventilation frequently promotes the maintenance of the same level as during two-lung ventilation without PEEP.[13,14] This type of mechanical ventilation may lead to overdistension of the remaining aerated lung regions and increase the shear forces generated during repetitive opening and collapse of atelectatic areas.[15,28] Furthermore, during OLV in lateral decubitus, the compression atelectasis of dependent lung regions, the loss of elastic recoil after thoracotomy, and mediastinal surgical manipulations can markedly reduce the aerated lung capacity, impair ventilation distribution, and worsen ventilation/perfusion mismatch.[29–31] Consequently and because potential benefit on inflammatory reaction with reduced V_T during OLV has been reported in a recent experimental study,[15] a decrease in V_T to 5 ml/kg was realized in the PV group. Based on previous results regarding the influence of PEEP during both two-lung[32] and one-lung ventilation,[33] a moderate level of PEEP was added in the PV group throughout the operative time. Because no previous clinical study about the influence of reduction of V_T on the perioperative proinflammatory response has demonstrated any advantage during two-lung ventilation, the same level of 9 ml/kg was maintained in both groups during this period.[9,10]

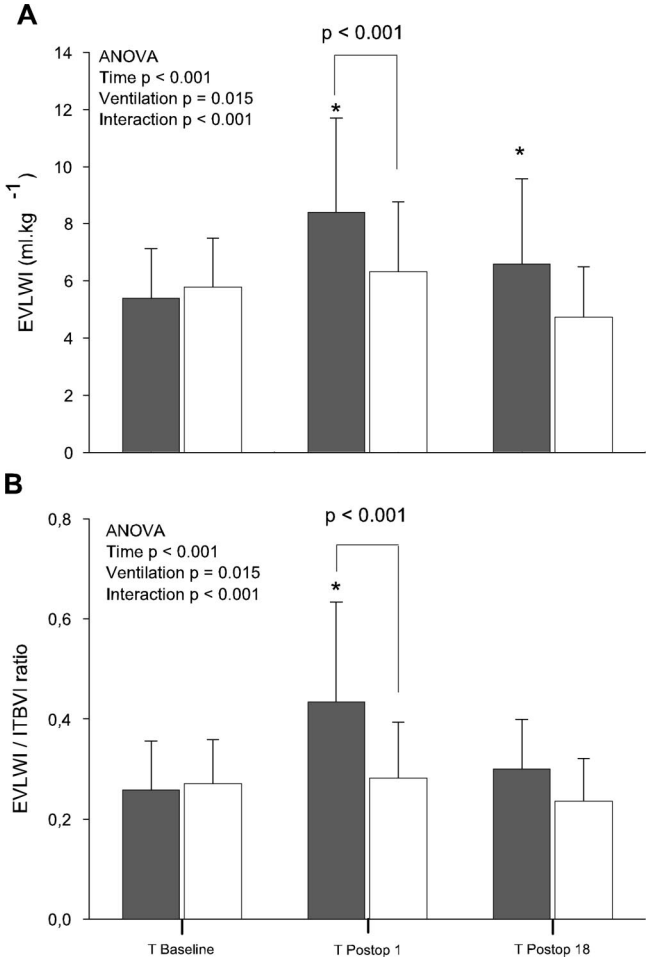

Fig. 4. Time course of extravascular lung water indexed to the body weight (EVLWI) (*A*) and EVLWI to intrathoracic blood volume indexed to the body weight (ITBVI) ratio (*B*) in conventional ventilation group (*gray bars*) and protective ventilation group (*white bars*) at baseline ($T_{Baseline}$), 1 h postoperatively ($T_{Postop\ 1}$), and 18 h postoperatively ($T_{Postop\ 18}$). Data are expressed as mean and SD. * $P < 0.01$ *versus* $T_{Baseline}$. ANOVA = analysis of variance.

Recent studies have demonstrated the clinical relevance of the proinflammatory cytokine response in the postoperative course of esophagectomy as predictive of cardiac or pulmonary complications such as acute respiratory distress syndrome.[1,19,34] The prolonged half-life of IL-6 and the related ease of detecting circulating level has made this cytokine a precious indicator of both duration and extent of surgical injury.[1,3,19,20] Moreover, because IL-6 seems to be a good marker of ventilator-induced injury,[21,35] this cytokine was chosen as the most reliable marker of the perioperative proinflammatory response in the studied setting. Because TNF-α, IL-1β, and IL-8 are

Table 3. *(Continued)*

	$T_{Postop\ 1}$		$T_{Postop\ 18}$		ANOVA		
	CV	PV	CV	PV	Time	Ventilation	Interaction
RR, V_T/min	12 ± 2	13 ± 2	—	—	< 0.001	< 0.05	< 0.01
V_T, ml	567 ± 55	542 ± 66	—	—	< 0.001	< 0.05	< 0.05
Pplat, cm H_2O	19.5 ± 5†	19 ± 2†	—	—	< 0.001	< 0.001	< 0.001
Arterial pH	7.34 ± 0.04§	7.32 ± 0.09§	7.34 ± 0.07§	7.36 ± 0.06§	< 0.05	< 0.01	NS
$Paco_2$, mmHg	39 ± 5	41 ± 5	43 ± 5†	42 ± 5†	< 0.005	< 0.01	NS
MAP, mmHg	85 ± 11	82 ± 14	76 ± 13	74 ± 14	NS	NS	NS
HR, beats/min	94 ± 16†	94 ± 19†	81 ± 13†	80 ± 15†	< 0.01	NS	NS
CI, $l \cdot min^{-1} \cdot kg^{-1}$	3.3 ± 0.9†	3.5 ± 1.2†	3.4 ± 0.7†	3.4 ± 0.9†	< 0.001	NS	NS

Data are expressed as mean ± SD.

* $P < 0.01$ *vs.* conventional ventilation. † $P < 0.01$ *vs.* $T_{Baseline}$. ‡ $P < 0.001$ *vs.* conventional ventilation. § $P < 0.05$ *vs.* $T_{Baseline}$.

CI = cardiac index; CV = conventional ventilation; HR = heart rate; MAP = mean arterial pressure; $Paco_2$ = arterial blood carbon dioxide tension; Pplat = plateau airway pressure; PV = protective ventilation; RR = respiratory rate; T_{Abdo} = end of abdominal time; $T_{Baseline}$ = baseline time; $T_{OLV\ 15}$and $T_{OLV\ End}$ = 15 min after initiation and at the end of one-lung ventilation, respectively; $T_{Postop\ 1}$ and $T_{Postop\ 18}$ = 1 and 18 h after the end of the surgical procedure, respectively; V_T = tidal volume.

equally implicated in the proinflammatory response, induced changes were also analyzed. However, there is evidence that these last are either rapidly cleared after the surgical injury with a related risk to miss the increase (TNF-α and IL-1β) or released to a lesser extent (IL-8).[2,20,36] The changes in cytokine level that we observed in the CV group were in accord with previous studies especially for IL-6 and IL-8.[20,37,38] Conversely, the increases of IL-6 that we observed in the PV group were lower and closer to the ones reported after gastrectomy, a moderately stressed procedure.[38] The absence of TNF-α increase could be explained by the time points at which we sampled the blood. Indeed, the TNF-α level was shown to peak early, with a short half-life after the inflammatory hit.[2] Other explanations could be an early inactivation of TNF-α in the circulation,[39] a limited implication of this cytokine in this setting,[40] or both. The persistent elevation in proinflammatory cytokines (*i.e.*, IL-1β, IL-6, and IL-8) observed in the CV group suggests that this strategy may delay or preclude the resolution of the systemic inflammatory process. Indeed, although our study protocol did not include the measurements of pulmonary cytokines, the influence of the ventilatory strategy on systemic cytokine levels that we observed is supported by previous data.[11,15,41] Recent experimental studies using normal lungs have shown a systemic cytokine response to injurious ventilatory strategies through a mechanotransduction mechanism, a loss of alveolar compartmentalization, or both.[11,42–44] It is likely that a CV strategy including a prolonged period of OLV may enhance the inflammatory response after major surgical procedures such as esophagectomy realizing a two-hit model. In this model, no factor by itself (*i.e.*, surgical procedure and mechanical ventilation) induces a sufficient effect, but the combination of both factors acts synergistically to cause the changes of the immune response.[10] This hypothesis has been suggested to explain ventilation-induced lung injury in acute respiratory distress syndrome patients[45,46] and, more recently, the alteration of the immune response in children without lung pathology undergoing mechanical ventilation.[47] Finally, our differences in cytokine levels have been ob-

Table 4. Postoperative Evolution of the Patients

	Conventional Ventilation (n = 26)	Protective Ventilation (n = 26)	*P* Value
Patient without morbid event, n	9	12	0.57
Pneumonia, n	10	6	0.37
Septic shock, n	6	4	0.72
ARDS, n	6	3	0.30
Supraventricular arrhythmia, n	4	4	1.00
Myocardial ischaemia, n	1	1	1.00
Renal failure, n	3	2	1.00
Anastomotic leak, n	2	1	1.00
Surgical reintervention, n	1	3	0.61
Postoperative ventilation duration, min*	171 ± 57	115 ± 38	< 0.001
ICU duration of stay, days	8 (5–14)	4 (3–11)	0.09
Days alive and discharged from the hospital at day 30	3.9 ± 5.7	5.1 ± 6.1	0.32
Postoperative mortality	1	2	1.00

Data are expressed as mean ± SD or median (interquartile range).

* From intensive care unit (ICU) admission to extubation.

ARDS = acute respiratory distress syndrome; renal failure = serum creatinine > 300 μM or need for hemofiltration.

served while the CV strategy was associated with plateau pressure not greater than 30 cm H_2O. This result suggests that an injurious ventilatory strategy is not necessarily associated with increased pressure and that a benefit in reducing V_T could be expected regardless of the plateau pressure before V_T reduction as recently suggested for acute respiratory distress syndrome patients.[48]

Another relevant finding of this study was the contemporary association of an increase in extravascular lung water, pulmonary permeability, and cytokine peak levels. Increases both in pulmonary microvascular permeability and in plasmatic concentration of cytokines have been reported in patients who developed pulmonary insufficiencies such as acute lung injury and acute respiratory distress syndrome after esophagectomy.[4,34] Our results suggest that this phenomenon can be attenuated by a PV strategy. Such a limitation has been previously demonstrated in experimental models of two-lung[43,49,50] and one-lung ventilation[15] but never in clinical conditions with previously healthy lungs. The better preservation of oxygenation in the protective group could also be attributed to this limitation in EVLWI amount associated with less ventilation/perfusion mismatch.

Potential limitations worth consideration include the small number of patients studied in a single institution, limiting the generalizability of the conclusions. Moreover, because we did not measure cytokines in the alveolar space, a comparison between alveolar and plasmatic concentrations of these biomarkers could not be made. The PV strategy reduced the duration of postoperative mechanical ventilation. The influence of ventilation duration on the occurrence of postoperative pulmonary complications has been previously reported,[51] whereas the clinical relevance of our results (less than 1 h difference) could seem limited. Moreover, although the incidence of relevant postoperative complications was in accord with previous reports,[5,52,53] our results have not demonstrated significant difference between groups. However, this study was not powered for clinical endpoints, and further studies should be performed to assess the influence of such a strategy on clinical outcomes. Another limitation was the inability in determining the respective influence of each component of the protective strategy (*i.e.*, reduced V_T and PEEP). We have previously demonstrated the influence of PEEP during OLV on alveolar recruitment and oxygenation preservation.[33] One can argue that this related effect of PEEP could rather explain the extubation being earlier than the reduction of V_T. However, recent data suggest that lower plateau pressure and reduced V_T are independently associated with a decrease in ventilator-induced lung injury.[48]

In summary, this study first demonstrates that mechanical ventilation strategy influences the proinflammatory systemic response during and after a complex surgical procedure requiring a prolonged period of OLV. The beneficial effects of a PV strategy based on the reduction of V_T during the OLV period associated with a moderate level of PEEP must be considered for high-risk surgical procedures such as esophagectomy.

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