Sevoflurane Ameliorates Local Immune Response to One-lung Ventilation during Chest Surgery for Cancer Lung

Ibrahim Kasb MD,

Talal Reda MD[1],

Ahmed Abdalla MD[2] &

Adel El-Khouly MD[3]

Objectives: **To determine the local and systemic immune response (IR) to open chest surgery using one-lung ventilation (OLV) during either propofol intravenous or sevoflurane inhalational anesthesia.**

Patients & Methods: **The study included 56 patients undergoing thoracotomy and resection for lung cancer; patients were divided into two equal groups: Group P received propofol infusion and Group S received sevoflurane inhalation with OLV using 100% oxygen and a tidal volume of 8-10 ml/kg at a rate to maintain the $PaCO_2$ between 35 and 40 mmHg. Bilateral broncho-alveolar lavage (BAL) was performed in all patients in supine position after intubation and at end of surgery. Synchronously, venous blood sample was obtained and then serum was separated. The BAL fluid of both sides and serum samples were ELISA assayed for estimation of interleukin (IL)-1β, IL-6, IL-10 and tumor necrosis factor (TNF)-α levels.**

Results: **Propofol anesthesia allowed significantly lower blood pressure measures and heart rate both during two-lung and one-lung ventilation compared to sevoflurane anesthesia. At the end of surgery, serum and BAL fluid levels of pro- and anti-inflammatory cytokines were significantly higher compared to levels estimated prior to surgery and irrespective of anesthetic modality used. Local IR was more fulminate than the systemic IR manifested as significantly higher BAL levels of cytokines estimated at the end of surgery compared to serum levels. Sevoflurane significantly modulated the local pulmonary IR as manifested by significantly lower BAL levels of TNF-α, IL-1β and IL-6 with significantly higher levels of IL-10 in both lungs at the end of surgery compared to propofol group.**

Conclusion: **Open chest surgery using OLV triggers vigorous inflammatory response in both ventilated and collapsed lungs. This response was manifested at the end of surgery and was more pronounced locally than systemically. Sevoflurane inhalational anesthesia significantly suppressed such local immune response compared to propofol and is advocated for anesthesia for chest surgery.**

KEYWORDS: **One-lung ventilation, Lung resection, Sevoflurane, Propofol, Broncho-alveolar lavage, Cytokines levels**

One-lung ventilation (OLV) has become a standard procedure for many interventions in thoracic surgery with a need for deflation of the lung to facilitate the surgical procedure. Experimental and clinical studies have shown that mechanical ventilation with increased tidal volume and airway pressure can induce a pro-inflammatory reaction in ventilated lung. However, only limited data exist on inflammatory alterations in the temporarily non-ventilated and thus atelectatic lung in patients undergoing thoracic surgery [1,2,3].

One-lung ventilation strategy initiates a series of patho-physiologic events that can be attributed to two major factors, namely hypoxia and re-oxygenation. The cellular damage that follows the oxygen deprivation is exacerbated during the re-oxygenation by the generation of free radicals. OLV in animals has been accepted as an ideal model to produce lung injury associated with organ failure and high mortality levels. The control of the pulmonary inflammation resulting from thoracic surgical manipulations has been a great challenge. Although some pharmacological treatments aiming to suppress the acute lung injury or acute respiratory distress syndrome has been used,

Departments of Cardiothoracic Surgery Benha & Cairo[1] Universities.

Departments of Anesthesia[2] & Clinical Biochemistry[3], Faculty of Medicine, Benha University.

Codex : o4/03/1307

many specific therapies have not proved beneficial, such as mortality reduction [4, 5, 6].

Sevoflurane is a highly fluorinated methyl-isopropyl ether widely used for induction and maintenance of general anesthesia. In addition to its anesthetic properties, it has also shown to be involved in protective mechanisms in conditions of hypoxia or endotoxemia, mostly studied in neuronal and myocardial tissues. Moreover, sevoflurane pretreatment during endotoxin-induced shock in rats significantly improved systolic blood pressure, acid–base balance and reduced mortality rates and plasma levels of tumor necrosis factor alpha (TNF-□) and interleukin-6 (IL-6), thus showing an attenuation of the inflammatory response [7, 8, 9].

Tissue injury causes the release of pro-inflammatory cytokines such as TNF-□ and IL-1β which are involved in many aspects of inflammation. Resident cells such as macrophages, mast cells and lymphocytes are able to release large amounts of TNF-□ and IL-1ß after stimulation by exogenous inflammatory stimuli and/or endogenous mediators, such as lipopolysaccharide and enterotoxins [10, 11, 12].

The produced TNF-□ triggers the release of a cascade of cytokines, which mediate the release of prostaglandins and sympathomimetic amines. Indeed, TNF-□ stimulates the production of IL-1ß and IL-6, which in turn stimulate the production of cyclooxygenase products and IL-8/neutrophil chemoattractant-1 thereby enhancing the production of sympathomimetic amines [13, 14]. IL-6 is also able to promote T-helper 2 (Th2) phenotypic responses and its actions can be classified as both pro- and anti-inflammatory. The local balance of IL-6 and IL-10 is an important determinant of subsequent immune responses. The Th2 responses predominate in critically ill patients and after surgery [15].

The current prospective comparative study aimed to determine the local and systemic immune response to open chest surgery using one-lung ventilation during either propofol intravenous anesthesia or sevoflurane inhalational anesthesia.

Patients & Methods

The current study was conducted at Departments of Chest Surgery and Anesthesia, Naser Insurance Institute since Jan 2010 till April 2013. After approval of the study protocol by the Local Ethical Committee and obtaining written fully informed patients' consent; 56 patients undergoing thoracotomy and resection for lung cancer were enrolled in the study. Exclusion criteria were patients assigned for pneumonectomy or minimal invasive procedures, patients had immunomodulating disease states other than the pulmonary pathology, patients maintained on immunosuppressant drugs. Patients were divided into two groups according to maintenance anesthesia used: Group P (n=28) received propofol infusion and Group S (n=28) received sevoflurane inhalation.

Anesthetic procedure

Anesthetic procedure was standardized for all patients including the use of double-lumen endobronchial tubes under fiber-optic control to allow single lung ventilation. All patients were taken into the operating room unpremedicated and after standard monitoring with non-invasive blood pressure, electrocardiography and peripheral oxygen saturation (SpO_2); administration of Lactated Ringer's solution was started. Patients were positioned in the lateral decubitus and after identification of the epidural space using the loss of resistance technique, a 20 gauge epidural catheter (Perifix 401, B. Braun, Melsungen AG) was inserted through an 18-gauge Tuohy needle that was placed at the T_{9-10} interspace and advanced 3 to 5 cm into the epidural space. After injection of 3 ml of 2% xylocaine through the epidural catheter as a test dose, the catheter was fixed and the patient was repositioned supine. Continuous epidural infusion of bupivacaine 0.125% was injected at time of induction of anesthesia prior to skin incision to act as preemptive analgesia and was continued as intraoperative and postoperative analgesia.

Anesthesia was induced by a bolus of remifentanil (1 μg/kg) followed by propofol (1-2 mg/kg) and vecuronium was given in dose of 1 mg/kg to facilitate tracheal intubation and was continued throughout duration of surgery. All patients received remifentanil-based maintenance anesthesia by slow remifentanil 0.05 to 0.25 μg/kg/min for remifentanil infusion in addition to propofol infusion 100 μg/kg/min of propofol in Group P or 1-2% sevoflurane in Group S.

After the induction of anesthesia, an arterial catheter was placed in the radial artery, and a central venous line (two lumens 20 cm long) was applied. After clinical confirmation of correct double-lumen tube placement (by inspection and auscultation) with the patient in both the supine and lateral decubitus positions ventilation was controlled by using 100% oxygen and a tidal volume of 8-10 ml/kg at a rate to maintain the $PaCO_2$ between 35 and 40 mmHg. Effective lung isolation was determined by the absence of a leak from the non-ventilated lumen of the endobronchial tube. When the pleura was opened, the isolation was confirmed by direct observation of the collapsed non-ventilated lung and the absence of leak from this lung.

Blood samples were withdrawn simultaneously from the distal central venous lumen and arterial catheters and analyzed within 5 min for measurement of arterial and venous blood gases. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were measured, always with the patient in the lateral position, in three phases: during two-lung ventilation (TLV), 15 min and 30 minutes after beginning of OLV (OLV_{15} and OLV_{30}). These measurements were made before ligation or division of any pulmonary vessels or bronchi. The duration of surgery, the duration of OLV, the amount of intraoperative blood loss, type of tumor and extent of resection were recorded.

Operative techniques

With the patient lying in the lateral decubitus position, a postero-lateral thoracotomy was made and pleural cavity was entered either through the fourth or the fifth intercostal space. The lobe to be resected was mobilized by preparation of the hilum and the interlobar fissures. Systematic mediastinal lymph node dissection was performed, then the tumor was resected either by a lobectomy, a bi-lobectomy, a sleeve-lobectomy or by an anatomical segmentectomy using staplers for the vascular, bronchial and parenchymal resection. After completing the systematic lymph node dissection, the pleural space was drained using one or two intercostal tubes. After ensuring proper hemostasis, wound closure was done.

Samples collection

Bilateral broncho-alveolar lavage (BAL) was performed in all patients in supine position after intubation and at end of surgery. The BAL fluid was immediately centrifuged at 2500 rpm for 15 minutes and the supernatant stored at -20°C. Synchronously, at time of obtaining BAL sample, a venous blood sample was collected under complete aseptic conditions in clean dry tube and allowed to clot and then serum was separated in clean dry Eppendorff tube to be stored at -80°C till assayed. The BAL of both sides and serum samples were assayed for ELISA estimation of levels of IL-1β [16], IL-6 [17], IL-10 [18] and TNF-α [19].

Statistical analysis

Sample Power was calculated according to Kraemer & Thiemann [20] using the proposed figure showed the sample size for 60% power would require an N of 26/group and 80% power would require an N of 31/group. This hypothesis was documented by Murphy & Myors [21]. Thus the current study sample size was chosen to be 28 patients per group. Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon; ranked test for unrelated data (Z-test) and Chi-square test (X^2 test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

The study included 56 patients; 41 males (73.2%) and 15 females (26.8%) with mean age of 59±10.8; range: 30-73 years. Mean duration of disease was 3.9±0.4; range: 3-5 years. Mean body mass index was 31.8±3.2; range: 24.4-37.6 kg/m^2. Thirty-two patients were ASA grade II, 20 patients were ASA grade III and only 4 patients were ASA grade I. There was non-significant (p>0.05) difference between both groups as regards demographic and preoperative data, (Table 1).

Forty-two patients (75%) had lobectomy, 6 patients (10.7%) had sleeve lobectomy and 5 patients (8.9%) had segmentectomy, while only 3 patients (5.4%) required bi-lobectomy. Mean duration of surgery was 197.2±24.7; range: 135-240 minutes;

		Total	Group P	Group S	P value
Age (years)		59±10.8 (30-73)	59.6±10.2 (35-73)	58.4±11.6 (30-70)	P>0.05 (=0.676)
Gender	Male	41 (73.2%)	21 (75%)	20 (71.4%)	P>0.05 (=0.429)
	Female	15 (26.8%)	7 (25%)	8 (28.6%)	
Duration of disease (years)		3.9±0.4 (3-5)	4±0.5 (3-5)	3.8±0.3 (3.5-4.2)	P>0.05 (=0.676)
Body weight (kg)		89.3±6.5 (73-97)	89.2±7.1 (73-97)	89.4±6 (78-95)	P>0.05 (=0.838)
Body height (cm)		167.8±5 (159-182)	168.1±5.5 (159-182)	167.5±4.6 (160-180)	P>0.05 (=0.760)
Body mass index (kg/m^2)		31.8±3.2 (24.4-37.6)	31.7±3.5 (24.4-37.1)	31.9±2.9 (26.7-37.6)	P>0.05 (=0.936)
ASA grade	I	4 (7.1%)	2 (7.1%)	2 (7.1%)	P>0.05 (=2.575)
	II	32 (57.1%)	14 (50%)	18 (64.3%)	
	III	20 (35.8%)	12 (42.9%)	8 (28.6%)	

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis. ASA:

Table 1. Patients' enrolment data

mean duration of OLV was 178.6±25.5; range: 120-225 minutes and mean amount of intraoperative blood loss was 437.2±121.9; range: 250-710 ml. As regards the type of tumor; 34 patients (60.8%) had adenocarcinoma, 11 patients (19.6%) had large cell carcinoma and another 11 patients (19.6%) had squameous cell carcinoma. There was non-significant (p>0.05) difference between both groups as regards operative data and type of tumor, (Table 2).

Baseline hemodynamic data showed non-significant (p>0.05) difference between patients of both study groups. However, propofol anesthesia allowed significantly (p<0.001) lower blood pressure measures and heart rate both during two-lung and one-lung ventilation compared to sevoflurane anesthesia, (Table 3).

		Total	Group P	Group S	P value
Surgical procedures	Lobectomy	42 (75%)	20 (71.5%)	22 (78.6%)	p>0.05 (=0.119)
	Bi-lobectomy	3 (5.4%)	2 (7.1%)	1 (3.6%)	
	Segmentectomy	5 (8.9%)	3 (10.7%)	2 (7.1%)	
	Sleeve lobectomy	6 (10.7%)	3 (10.7%)	3 (10.7%)	
Duration of surgery (minutes)		197.2±24.7 (135-240)	196.2±22.7 (145-225)	198.1±26.9 (135-240)	P>0.05 (=0.129)
Duration of lung ventilation (minutes)		178.6±25.5 (120-225)	178.4±23.8 (125-215)	178.9±27.5 (120-225)	P>0.05 (=0.600)
Amount of intraoperative blood loss (ml)		437.2±121.9 (250-710)	399.6±92.2 (250-540)	474.8±137.2 (300-710)	P>0.05 (=1.843)
Type of tumor	Large cell carcinoma	11 (19.6%)	6 (21.4%)	5 (17.9%)	p>0.05 (1.451)
	Adenocarcinoma	34 (60.8%)	18 (64.3%)	16 (57.1%)	
	Squameous cell cancer	11 (19.6%)	4 (14.3%)	7 (25%)	

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis

Table 2. Operative data

		Group P	Group S	Statistical significance
HR (beats/min)	Baseline	81.3±3.7	80.8±3.4	p>0.05
	TLV	73.6±3.4	76±5.9	p<0.05
	OLV_{15}	69.4±3	76.4±5.4	P<0.001
	OLV_{30}	68.3±3.4	76.6±5.9	P<0.001
SBP (mmHg)	Baseline	114.8±6.5	114±5.6	p>0.05
	TLV	92.2±6.9	104.3±6.8	p<0.001
	OLV_{15}	88.5±8.5	100±5.6	P<0.001
	OLV_{30}	83.4±6.9	95.7±5.1	P<0.001
DBP (mmHg)	Baseline	81.3±4.6	81.7±3.8	p>0.05
	TLV	75.9±3.6	77.8±3.2	p<0.001
	OLV_{15}	74.3±2.3	76.1±2.5	P<0.001
	OLV_{30}	72.8±2.4	74.6±2.1	P<0.001
MAP (mmHg)	Baseline	92.4±4.2	92.5±3.6	p>0.05
	TLV	81.3±3.5	86.5±3.1	p<0.001
	OLV_{15}	79±3.4	84±2.3	P<0.001
	OLV_{30}	76.4±2.7	81.6±2.2	P<0.001

Data are presented as mean±SD; TLV: two-lung ventilation; OLV: one-lung ventilation; HR: Heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure

Table 3. Intraoperative hemodynamic data during two-lungs and one-lung ventilation at 15- and 30-minutes compared to baseline data

Baseline serum levels and BAL levels of either the ventilated (BAL-V) or collapsed (BAL-C) lung of estimated cytokines showed non-significant (p>0.05) difference between both groups. Estimated serum TNF-α levels at the end of surgery were significantly (p<0.05) higher compared to that estimated prior to surgery with non-significantly (p>0.05) higher serum levels in patients of group P compared to group S. Mean BAL-C levels of TNF-α estimated at the end of surgery were significantly (p<0.05) higher in both groups compared to levels estimated prior to surgery with non-significantly (p>0.05) higher levels in group P compared to group S. On the other hand, mean BAL-V levels of TNF-α estimated at the end of surgery were significantly (p<0.05) higher in both groups compared to levels estimated prior to surgery with significantly (p<0.05) higher levels in group P compared to group S. Moreover, BAL levels of TNF-α estimated at the end of surgery in collapsed lung were non-significantly (p>0.05) higher, but were significantly (p<0.05) higher in ventilated lung compared to serum levels of the same patients, (Table 4, Fig. 1).

Estimated serum IL-1β levels at the end of surgery were significantly (p<0.05) higher compared to that estimated prior to surgery with non-significantly (p>0.05) higher serum levels in group P compared to group S. Mean BAL-V levels of IL-1β estimated at the end of surgery were significantly (p<0.05) higher in both groups compared to levels estimated prior to surgery with significantly (p<0.05) higher levels in group P compared to group S. On the other hand, mean BAL-C levels of IL-1β estimated at the end of surgery were significantly (p<0.05) higher in group P, but were non-significantly (p>0.05) higher in group S compared to levels estimated prior to surgery with significantly (p<0.05) higher levels in group P compared to group S. In both groups, mean BAL levels of IL-1β were significantly higher in ventilated lung compared to collapsed lung. Moreover, in group P, BAL levels of IL-1β estimated at the end of surgery both in collapsed and ventilated lungs were significantly (p<0.05) higher compared to serum levels of the same patients. On contrary, in group S, BAL levels of IL-1β estimated at the end of surgery were significantly (p<0.05) higher in ventilated lung, but non-significantly higher in collapsed lung compared to serum levels of the same patients (Table 4, Fig. 2).

Estimated serum IL-6 levels at the end of surgery were significantly (p<0.05) higher compared to that estimated prior to surgery with non-significantly (p>0.05) higher serum levels in group P compared to group S. Mean bilateral BAL levels of IL-6 estimated at the end of surgery were significantly (p<0.05) higher in both groups compared to levels estimated prior to surgery. Mean BAL-V level of IL-6 estimated at the end of surgery in group P was significantly (p<0.05) higher compared to group S, while mean BAL-C levels showed non-significant (p>0.05) difference between both groups despite being lower in group S. Moreover, bilateral BAL levels of IL-6 estimated at the end of surgery in both groups were significantly (p<0.05) higher compared to serum levels of the same patients (Table 4, Fig. 3).

Estimated serum IL-10 levels at the end of surgery were significantly (p<0.05) higher compared to that estimated prior to surgery with significantly (p<0.05) higher serum levels in group S compared to group P. Mean bilateral BAL levels of IL-10 estimated at the end of surgery were significantly (p<0.05) higher in both groups compared to levels estimated prior to surgery with significantly (p<0.05) higher levels in group S compared to group P. Mean BAL-V level of IL-10 estimated at the end of surgery in group S was significantly (p<0.05) higher compared to its level in BAL-C, while the difference was non-significant (p>0.05) in group P. Moreover, in group S, mean BAL levels of IL-10 estimated at the end of surgery in both lungs were significantly (p<0.05) higher compared to serum levels of the same patients; while in group P the difference was non-significant despite the higher BAL levels (Table 4, Fig. 4).

			Group P	Group S
TNF-α	Prior to surgery	Serum	2.3±0.66	2.25±0.65
		BAL-V	2.15±0.56	2.13±0.46
		BAL-C	2.1±0.51	2.08±0.53
	After surgery	Serum	3.2±1.13[a]	2.93±0.9[a]
		BAL-V	6.4±1.4[acd]	4.87±1.35[abcd]
		BAL-C	3.4±0.89[a]	3.14±0.97[a]
IL-1β	Prior to surgery	Serum	8.82±5.52	8.39±5.24
		BAL-V	10.86±4.21	11.21±7.5
		BAL-C	11±4.41	12±3.69
	After surgery	Serum	17.64±5.94[a]	13.93±4.79[a]
		BAL-V	59.14±30.52[acd]	17.86±4.26[abcd]
		BAL-C	26.75±14.9[ad]	13.14±3.17[b]
IL-6	Prior to surgery	Serum	16.5±6.3	19.3±8.7
		BAL-V	14.2±8	17.6±8.8
		BAL-C	16.2±8.5	15.5±5.7
	After surgery	Serum	24.9±6.5[a]	22.1±8.4[a]
		BAL-V	62.1±17[acd]	53.6±10.7[abd]
		BAL-C	55.6±14.8[ad]	50±19[ad]
IL-10	Prior to surgery	Serum	21.9±5.6	23±5.3
		BAL-V	23.3±7.8	25.7±6.9
		BAL-C	23.5±6.3	24.9±5.9
	After surgery	Serum	39.5±8.9[a]	49.9±11.3[ab]
		BAL-V	47±14.2[a]	68±12.1[abcd]
		BAL-C	43.2±11.8[a]	63.1±8.1[abd]

Data are presented as mean±SD; BAL-V: Broncho-alveolar lavage of ventilated lung; BAL-C: Broncho-alveolar lavage of collapsed lung; Preop.: Preoperative; PO: postoperative; TNF-α: Tumor necrosis factor-α; IL-6: Interleukin-6; [a]: significance versus preoperative level; [b]: significance versus Group P; [c]: significance versus BAL-C; [d]: significance versus serum level.

Table 4. Mean serum and BAL levels of studied cytokines in both studied groups estimated prior to and after surgery

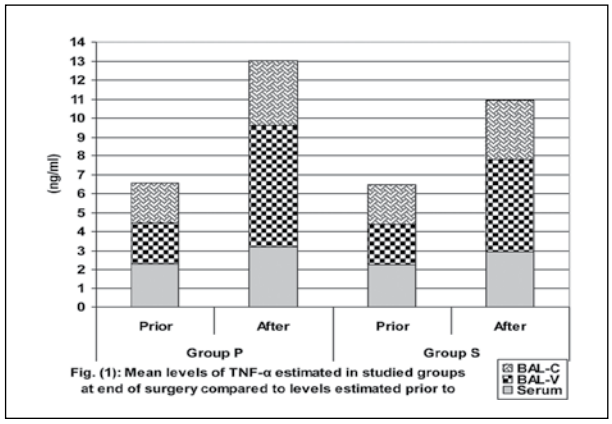

Fig. (1): Mean levels of TNF-α estimated in studied groups at end of surgery compared to levels estimated prior to

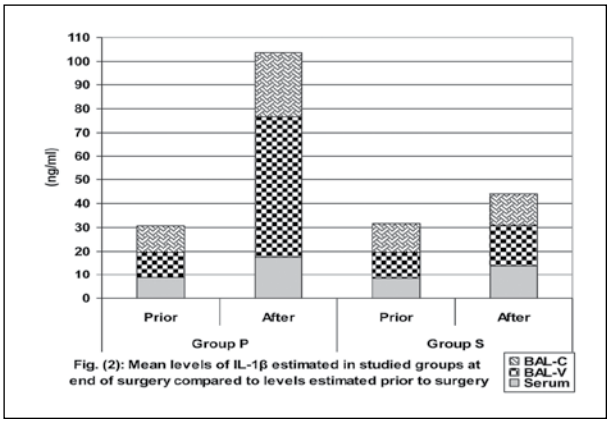

Fig. (2): Mean levels of IL-1β estimated in studied groups at end of surgery compared to levels estimated prior to surgery

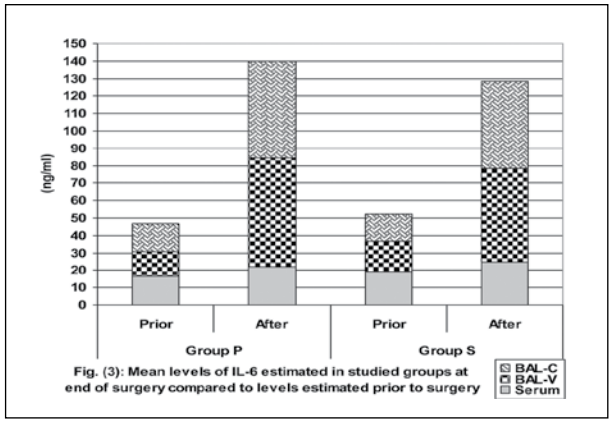

Fig. (3): Mean levels of IL-6 estimated in studied groups at end of surgery compared to levels estimated prior to surgery

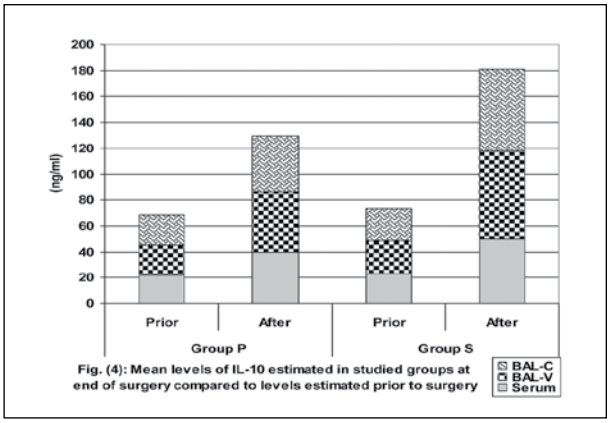

Fig. (4): Mean levels of IL-10 estimated in studied groups at end of surgery compared to levels estimated prior to surgery

Discussion

The current study showed that chest surgery triggers a vigorous systemic inflammatory response (IR) manifested as significantly higher levels of both pro- and anti-inflammatory cytokines estimated at the end of surgery in serum and locally in BAL and irrespective of anesthetic modality used. Moreover, the local IR was more fulminate than the systemic IR manifested as significantly higher BAL levels of cytokines estimated at the end of surgery compared to serum levels.

These findings supported that previously reported in literature concerning the impact of open chest surgery on IR; **Walker & Leaver** [22] documented that conventional open major surgery evokes an injury response involving endocrine, neural, and immunologic mechanisms with the immunologic responses are characterized by release of cytokines, inflammatory mediators, and acute-phase proteins and by adverse disturbances in immune cell function. **Bobocea et al.** [23] reported that prospective thoracoscopic lobectomy trials found better preservation of lymphocyte T-cell function and quicker return of proliferative responses to normal, lower levels of CRP, thromboxane and prostacyclin and concluded that immune function is influenced by the extent of surgical trauma. Also, **Leite et al.** [24] experimentally detected that OLV significantly increased myeloperoxidase activity in the collapsed and continuously ventilated lungs (31% and 52% increase, respectively) and serum IL-6 and CRP levels were markedly higher in OLV group compared with control.

The current study reported significantly higher BAL levels estimated at the end of surgery in ventilated lung compared to collapsed lung. These data indicated a possible role for OLV as a stimulant for IR exaggeration. In support of these findings; **Zingg et al.** [25] reported that both the ventilated and the collapsed lungs during OLV in transthoracic esophagectomy showed an inflammatory response which was more pronounced on the ventilated side and the response was already observed at the end of surgery, indicating a rapid reaction to the surgical and anesthetic trauma. **Breunig et al.** [26] found that both sides of the lung showed a significant increase in IL-6 and IL-1 receptor-A concentrations over time and concluded that the difference in extent of response underlines the complexity of the inflammatory processes during OLV. **Jonker et al.** [27] conducted clinical study for the impact of thoracic injury on local and systemic IR and found that injured patients had significantly higher BAL fluid and serum TNF-α, IL-1β, and IL-6 concentrations with greater increases in the BAL fluid

than in the serum and concluded that injury significantly increases human airway TNF-α, IL-1β, and IL-6 and increases are greater in the airway than in serum, implying a local rather than a systemic stress response to thoracic injury. **Leite et al.** [28] experimentally found that bronchial occlusion for 1 or 3 hours followed by lung re-expansion exhibited pulmonary edema formation and neutrophil recruitment as well as a higher myeloperoxidase activity with increased levels of IL-6, IL-1β, and TNF-α in BAL fluid in comparison with control rats.

Sevoflurane significantly ameliorated the effects ventilation on local pulmonary IR as manifested by significantly lower BAL levels of TNF-α, IL-1β and IL-6 in both lungs at the end of surgery in patients received sevoflurane compared to those received propofol. In support of these data; **De Conno et al.** [29] reported an immuno-modulatory role for the volatile anesthetic sevoflurane in patients undergoing OLV for thoracic surgery with significant reduction of inflammatory mediators and a significantly better clinical outcome during sevoflurane anesthesia with the increase of inflammatory mediators on OLV was significantly less pronounced in the sevoflurane group. **Schilling et al.** [30] reported that alveolar pro-inflammatory cytokines were increased in the ventilated lung after OLV and the mediator release was more enhanced during propofol anesthesia compared with desflurane or sevoflurane administration with significantly higher levels of TNF-α, IL-8 and IL-1β, whereas the systemic proinflammatory response was negligible, and concluded that OLV increases the alveolar concentrations of proinflammatory mediators in the ventilated lung, but both desflurane and sevoflurane suppress the local alveolar, but not the systemic inflammatory responses to OLV and thoracic surgery. **Sugasawa et al.** [31] reported that BAL levels of IL-1β, IL-6, and IL-8 were significantly increased in the dependent lung and the nondependent lung after OLV compared with baseline levels; moreover, IL-6 BAL level in the dependent lung was significantly higher in the propofol group than in the sevoflurane group after OLV and concluded that OLV induced inflammatory responses of the bronchial epithelia in both lungs during lung resection and this inflammatory response was significantly suppressed by sevoflurane compared with propofol and the anti-inflammatory effect of sevoflurane was more pronounced in the dependent lung than in the nondependent lung during OLV. **Schmid et al.** [32] tried to explore the immuno-modulatory action of sevoflurane and found that sevoflurane inhibits granulocyte activation during ex vivo extracorporeal circulation and therefore has the potential to decrease the triggered inflammatory response.

It could be concluded that chest surgery using OLV triggers vigorous inflammatory response in both ventilated and collapsed lungs. This response was manifested at the end of surgery and was more pronounced locally than systemically. Sevoflurane inhalational anesthesia significantly suppressed such local immune response compared to propofol and is advocated for anesthesia for chest surgery

References

1. Kuipers MT, Aslami H, Janczy JR, van der Sluijs KF, Vlaar AP, Wolthuis EK, Choi G, Roelofs JJ, Flavell RA, Sutterwala FS, Bresser P, Leemans JC, van der Poll T, Schultz MJ, Wieland CW: Ventilator-induced lung injury is mediated by the NLRP3 inflammasome. Anesthesiology. 2012;116(5):1104-15.
2. Fan E, Villar J, Slutsky AS: Novel approaches to minimize ventilator-induced lung injury. BMC Med. 2013; 28;11:85.
3. Biehl M, Kashiouris MG, Gajic O: Ventilator-Induced Lung Injury: Minimizing Its Impact in Patients With or at Risk for ARDS. Respir Care. 2013; 58(6):927-37.
4. Gothard J. Lung injury after thoracic surgery and one-lung ventilation. Curr Opin Anaesthesiol. 2006;19(1):5-10.
5. Tsai JA, Lund M, Lundell L, Nilsson-Ekdahl K. One-lung ventilation during thoracoabdominal esophagectomy elicits complement activation. J Surg Res. 2009;152(2):331-7.
6. Leite CF, Toro IFC, Antunes E, Mussi RK. Standardization of a method of prolonged thoracic surgery and mechanical ventilation in rats to evaluate local and systemic inflammation. Acta Cir Bras. 2011;26(1):38-43.
7. Li H, Wang JK, Zeng YM, Yang CX, Chen HT, Wen XJ, Shui CL, Liang H: Sevoflurane post-conditioning protects against myocardial reperfusion injury by activation of phosphatidylinositol-3-kinase signal transduction. Clin Exp Pharmacol Physiol 2008, 35:1043–1051.
8. Matchett GA, Allard MW, Martin RD, Zhang JH: Neuroprotective effect of volatile anesthetic agents: molecular mechanisms. Neurol Res 2009, 31:128–34.
9. Zitta K, Meybohm P, Bein B, Ohnesorge H, Steinfath M, Scholz J, Albrecht M: Cytoprotective effects of the volatile anesthetic sevoflurane are highly dependent on timing and duration of sevoflurane conditioning: findings from a human, in-vitro hypoxia model. Eur J Pharmacol 2010, 645:39–46.
10. Boraschi D, Cifone MG, Falk W, Flad HD, Tagliabue A and Martin MU: Cytokines in inflammation. Eur. Cytokine Netw. 1998, 9, 205–12.
11. Dinarello CA: Pro-inflammatory cytokines. Chest 2000, 118: 503-8.
12. Oppenheim JJ: Cytokines: past, present and future. Int. J. Hematol. 2001, 74, 3–8.
13. Ferreira SH, Lorenzetti BB, Bristow AF and Poole S: Interleukin-1 beta as a potent hyperalgesic agent antagonized by a tripeptide analogue. Nature, 1988; 334: 698–700.
14. Lorenzetti BB, Veiga FH, Canetti CA, Poole S, Cunha FQ and Ferreira SH: Cytokine-induced neutrophil chemoattractant 1 (CINC-1) mediates the sympathetic component of inflammatory mechanical hypersensitivity in rats. Eur. Cytokine. Netw. 2002; 13: 456–61.

15. Opree A and Kress M: Involvement of the proinflammatory cytokines tumor necrosis factor-a, IL-1b and IL-6 but not IL-8 in the development of heat hyperalgesia: effects on heat-evoked calcitonin gene-related peptide release from rat skin. J Neurosci 2000; 20: 6289–93
16. Dinarello CA: ELISA kits based on monoclonal antibodies do not measure total IL-1β synthesis. J Immunol Methods.; 148: 255–9, 1992.
17. Engvall E, Perlmann P: Enzyme-linked immunosorbent assay. Quantitation of specific antibodies by enzyme-labeled anti-immunoglobulin in antigen-coated tubes. J Immunol. 1972; 109: 129-35.
18. Taga K, Tosato G: IL10 inhibits human T cell proliferation and IL2 production. J Immunol. 1992; 148: 1143-8.
19. Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YCE, Mathison J, Ulevitch R, Cerami A: Identify of tumor necrosis factor and the macrophage secreted factor cachectin. Nature; 16: 552-4, 1985.
20. Kraemer HC, Theimann S: How many subjects? Statistical power analysis in research; 1987, Newbury Park, CA: Sage.
21. Murphy KR, Myors B: Statistical Power Analysis: A Simple and General Model for Traditional and Modern Hypothesis Tests; 2003, 2nd Ed., Lawrence Erlbaum Associates, Inc.
22. Walker WS, Leaver HA: Immunologic and stress responses following video-assisted thoracic surgery and open pulmonary lobectomy in early stage lung cancer. Thorac Surg Clin. 2007;17(2):241-9, ix.
23. Bobocea AC, Trandafir B, Bolca C, Cordoş I: Minimally invasive surgery in cancer. Immunological response. Chirurgia (Bucur). 2012; 107(2):154-7.
24. Leite CF, Calixto MC, Toro IF, Antunes E, Mussi RK: Characterization of pulmonary and systemic inflammatory responses produced by lung re-expansion after one-lung ventilation. J Cardiothorac Vasc Anesth. 2012;26(3):427-32.
25. Zingg U, Forberger J, Frey DM, Esterman AJ, Oertli D, Beck-Schimmer B, Zollinger A: Inflammatory response in ventilated left and collapsed right lungs, serum and pleural fluid, in transthoracic esophagectomy for cancer. Eur Cytokine Netw. 2010;21(1):50-7.
26. Breunig A, Gambazzi F, Beck-Schimmer B, Tamm M, Lardinois D, Oertli D, Zingg U: Cytokine & chemokine response in the lungs, pleural fluid and serum in thoracic surgery using one-lung ventilation. J Inflamm (Lond). 2011 Nov 11;8:32.
27. Jonker MA, Hermsen JL, Gomez FE, Sano Y, Kudsk KA: Injury induces localized airway increases in pro-inflammatory cytokines in humans and mice. Surg Infect (Larchmt). 2011; 12(1):49-56.
28. Leite CF, Marangoni FA, Camargo EA, Braga Ade F, Toro IF, Antunes E, Landucci EC, Mussi RK: Simvastatin attenuates neutrophil recruitment in one-lung ventilation model in rats. Acta Cir Bras. 2013; 28(4):245-50.
29. De Conno E, Steurer MP, Wittlinger M, Zalunardo MP, Weder W, Schneiter D, Schimmer RC, Klaghofer R, Neff TA, Schmid ER, Spahn DR, Z›graggen BR, Urner M, Beck-Schimmer B: Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. Anesthesiology. 2009; 110(6):1316-26.
30. Schilling T, Kozian A, Senturk M, Huth C, Reinhold A, Hedenstierna G, Hachenberg T: Effects of volatile and intravenous anesthesia on the alveolar and systemic inflammatory response in thoracic surgical patients. Anesthesiology. 2011; 115(1):65-74.
31. Sugasawa Y, Yamaguchi K, Kumakura S, Murakami T, Suzuki K, Nagaoka I, Inada E: Effects of sevoflurane and propofol on pulmonary inflammatory responses during lung resection. J Anesth. 2012; 26(1):62-9.
32. Schmid E, Krajewski S, Bachmann D, Kurz J, Wendel HP, Rosenberger P, Balkau B, Peter K, Unertl K, Straub A: The volatile anesthetic sevoflurane inhibits activation of neutrophil granulocytes during simulated extracorporeal circulation. Int Immunopharmacol. 2012;14(2):202-8.