Thoracotomy procedures effect cytokine levels after thoracoabdominal esophagectomy

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Abstract. Pulmonary complications together with surgical complications are the most frequent causes for morbidity and mortality after thoracoabdominal esophagectomy. The continuous improvement of surgical techniques has led to a decrease in surgical complications, whereas up to 30% of the patients develop postoperative pulmonary complications such as acute lung injury (ALI) or even the more severe acute respiratory distress syndrome (ARDS), which are characterized by an acute inflammation in the lung parenchyma and the airspace. Evidence from several studies indicates that a complex network of inflammatory cytokines and mediators play a key role in mediation, amplification, and perpetuation of the process of lung injury and that the thoracotomy itself is a risk factor for developing ALI or ARDS. In this trial, the cytokine levels of IL6, IL8 and IL10 were measured and compared in 30 patients who had undergone an extended radical thoracoabdominal esophagectomy for esophageal cancer, via anterolateral thoracotomy (n=17) or posterolateral thoracotomy (n=13). Patients of both groups were similar in terms of age, sex and preoperative pulmonary function as well as in the anesthetic procedures they have undergone. All patients displayed significantly increased serum levels of IL6 and IL8 after thoracoabdominal esophagectomy. However, patients who were subjected to an anterolateral thoracotomy were reported with significantly higher serum levels of IL6 and IL8 compared to patients who had received a posterolateral thoracotomy. Thus, the choice of the thoracotomy method during the thoracoabdominal esophagectomy and the resultant cytokine levels may contribute to the occurrence of postoperative pulmonary complications and may have an impact on the extent and severity of the surgical stress.

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Introduction

Cytokines act as messengers both within the immune system and between the immune system and other systems of the body, forming an integrated network that is highly evolved in the regulation of immune responses. After elective surgery an acute phase response is often observed which commonly results in an activation of the cytokine network as an important part of this response. In particular, IL6 has been shown to play a pivotal role of in the acute phase response after surgery (1-3), resulting in increased plasma levels which correlate with the extent and severity of the surgical stress (1,3).

Acute lung injury (ALI) and a more severe form, the acute respiratory distress syndrome (ARDS), are characterised by a diffuse inflammation and an increased alveolar-capillary membrane permeability that causes diffuse interstitial and alveolar oedema and persistent refractory hypoxemia (4). Evidence from several studies indicates that a complex network of inflammatory cytokines and chemokines has a leading role in mediation, amplification and perpetuation of the process of lung injury (5).

ARDS is one of the primary contributors to mortality in ICU patients. A wide variety of clinical conditions such as sepsis, burns, trauma and major surgery and esophageal resection in particular, constitute a predisposition for the development of ARDS (6-8).

The prognosis of esophageal cancer is generally poor because of its biological aggressiveness and anatomical characteristics. In order to improve the prognosis, an extended radical esophagectomy with radical lymphadenectomy is often performed. However, transthoracic esophagectomy with lymphadenectomy is well known as one of the most stressful gastrointenstinal operations, which considerably increases the amount of surgical stress (9,10). As a result, the operative morbidity rate is still high, despite recent improvements in the peri-operative management (11). Moreover, it has been reported that elevated plasma

cytokine levels correlate with postoperative morbidity and mortality rates (12,13). Sakamoto *et al* reported that plasma levels of IL6 after thoracic surgery, such as pneumonectomy and esophagectomy, were much higher than levels after abdominal surgery, such as pancreaticoduodenectomy and colorectal resection (14).

Among the postoperative complications after thoracoabdominal esophagectomy, pulmonary complications as well as anastomotic leakage tend to be the most critical (15,16). For instance, up to 30% of the patients after thoracoabdominal esophagectomy develop pulmonary complications such as ALI or even ARDS (17). Although a variety of insults may lead to ALI and ARDS, a common pathway may probably result in lung damage (18-20).

A complex series of inflammatory events have been recognized during the development of ARDS, but the exact sequence of the events remains unclear. Leukocyte activation and free radical release, proteases, arachidonic acid metabolites, inflammatory and anti-inflammatory cytokines result in the increased alveolar-capillary membrane permeability (21-24).

The activation of the cytokine network is crucial for the development of e.g. ALI or ARDS (4,6,25) and plasma cytokine levels are known to correlate with postoperative morbidity and mortality rates (12,13). To address this issue, we investigated the impact of the thoracic approach in thoracoabdominal esophagectomy on plasma cytokine levels. To our knowledge, anterolateral thoracotomy has not been compared to posterolateral thoracotomy with respect to trauma-related changes in the metabolism and immune response as measured in terms of cytokine production.

Thus, the present study was designed to quantify differences in surgical trauma between anterolateral and posterolateral thoracotomy during thoracoabdominal esophagectomy by measuring concomitant levels of IL6, IL8 and IL10 production.

Materials and methods

Patients. Approval for this investigation was gained from the ethics committee of the University of the Saarland. After informed consent was obtained, thirty consecutive patients undergoing esophagectomy for esophageal malignancies were included in this prospective trial between February 2002 and October 2005. According to the respective approach to the chest cavity patients were allocated into two groups. Group I consisted of 17 patients who had an anterolateral thoracotomy and group II included 13 patients who had a posterolateral thoracotomy. Biographical and disease-related data from all patients were prospectively entered into a data file (Table I). Operation data and data regarding the patient's stay in the intensive care unit (ICU) were retrospectively retrieved from an administrative data file (Table II). Blood samples were taken from each patient prior to surgery and immediately after operation. In addition, two blood samples were taken on the first and third postoperative days (POD).

Thoracotomy procedure

Anterolateral thoracotomy. Performing the anterolateral thoracotomy, the patient was placed in a supine position and the operative side was elevated 45˚ from the table by sliding a padded sand bag below the buttocks and back. The ipsilateral arm was placed on an elevated armrest. The skin incision followed the submammary fold and extends from the sternum anteriorly to the midaxillary line. The chest cavity was entered in the fourth or fifth intercostal space. Dissecting the dorsal mediastinum the lung was obtructed via spatula.

Posterolateral thoracotomy. To enter the chest cavity via posterolateral thoracotomy, the patient was placed in the appropriate complete lateral decubitus position. The incision followed the course of the underlying ribs, and extends from a point located ~8 cm from the mid-spinal line to the anterior axillary line, thus passing below the tip of the scapula.

Excluding criteria. Patients with chronic inflammatory diseases and patients with chronic viral infections such as hepatitis and HIV were not included.

Blood sampling and processing. Peripheral blood samples were collected in sterile heparinized tubes under sterile conditions. The samples were centrifuged at 1500 x g for 5 min and the plasma was stored at -80˚C until ELISA assays were performed.

Enzyme-linked immunosorbent assay of IL6, IL8 and IL10. Human IL6, IL8 and IL10 concentrations in the plasma were measured in duplicate using commercially available ELISA kits (Biosource Europe, Nivelles, Belgium) following the manufacturer's guidelines.

Statistical analysis. All cytokine concentrations are presented as mean and SEM (standard of the mean). All statistical calculations were done with the MedCalc software package (MedCalc Software, Mariakerke, Belgium) (26). The parametric Student's t-test was applied, if normal distribution was given, otherwise, the Wilcoxon's rank sum test was used. $p<0.05$ at an $\alpha<0.05$ was considered significant.

Results

Patients characteristics, perioperative cytokine levels and comparison of background factors. Prior to the thoracoabdominal esophagectomy, 30 patients were enrolled in this study over a 45-month period. Tables I and II summarize the biographic and operative data. Male (25, 83.3%) and female (5, 16.7%) patients were included in the study with a median age of 61 years (42-77). The interleukin expression was evaluated in all patients before surgery. There was a great variation in the serum levels of the analysed interleukin before the operation (IL6: 18.8±5.1 pg/ml, IL8: 6.6±1.3 pg/ml, IL10: 0.4±0.4 pg/ml).

A comparison between the anterolateral and posterolateral thoracotomy group revealed no differences in age, gender ratio, stage of disease or preoperative pulmonary function. Likewise, we observed no significant difference between the two groups in relation to thoracic operation time, but a difference in the amount of blood loss in the posterolateral thoracotomy group ($p<0.05$). Moreover, the two groups did not differ in terms of patients displaying respiratory insufficiency or ARDS. Finally, there was no difference between the two groups in intensive care unit stay and in-hospital stay. However, there were significant differences in IL6 and IL8 levels.

Table I. Biographic data of patients undergoing esophageal resection.

	Thoracoabdominal esophagectomy	
Procedure	Anterolateral thoracotomy	Posterolateral thoracotomy
N	17	13
Gender (men/women)	14/3	11/2
Age (years)	59 (42-76)	62 (47-77)
Smoking (+/-)	11/6	8/4
Tumour stage		
I	0	1
II	9	8
III	7	4
IV	1	0
Vital capacity (ml)	3650 (2900-5340)	4160 (1940-8710)
Forced expiratory volume in 1 sec (ml)	2645 (1645-4820)	2830 (1700-3870)
Squamous cell carcinoma	4	4
Adenocarcinoma	12	9
Neuroendocrine tumour	1	0
Localisation of the main tumour		
Mid esophagus (22-32 cm)	3	0
Lower esophagus (33-39 cm)	8	8
Cardia ventriculi	6	4
Neoadjuvant treatment	6	4

Table II. Operation data of patients undergoing esophageal resection.

	Thoracoabdominal esophagectomy	
Procedure	Anterolateral thoracotomy	Posterolateral thoracotomy
N	17	13
Operation time (min)	277 (198-384)	338 (249-398)
Blood loss (ml)	700 (100-4000)	460 (200-1050)
One Lung ventilation (min)	102 (68-244)	117 (72-180)
Respiratory insufficiency	6	4
Acute respiratory distress syndrome (ARDS)	1	1
Mortality	2	0
Intensive care unit stay (days)	15 (2-64)	11 (2-49)
In-hospital stay (days)	17 (8-74)	24 (12-65)

Postoperative IL6 levels after anterolateral and posterolateral thoracoabdominal esophagectomy. IL6 serum levels were examined postoperatively (Fig. 1). After anterolateral and posterolateral esophagectomy, circulating IL6 was significantly increased with a peak at the end of the surgery (Fig. 1a and b). Irrespective of the choice of the thoracotomy method we found significantly higher levels of IL6 at the end of the surgery on the first POD (POD1) and third POD (POD3) compared to the preoperative values ($p<0.01$). To determine whether the anterolateral or posterolateral thoracotomy had an impact on circulating IL6 we compared the results of the 17 patients which had an anterolateral thoracotomy to the 13 patients with posterolateral thoracotomy. Thus, in comparison to persons with posterolateral thoracotomy, anterolateral thoracotomy patients displayed significantly higher amounts of IL6 in the serum at the end of the surgery (729.5±110.8 pg/ml vs. 1349.2±209.8 pg/ml) as well as on POD1 (424.0±79.8 pg/ml vs. 956.5±255.7 pg/ml), respectively ($p<0.05$; Fig. 1c). In terms of

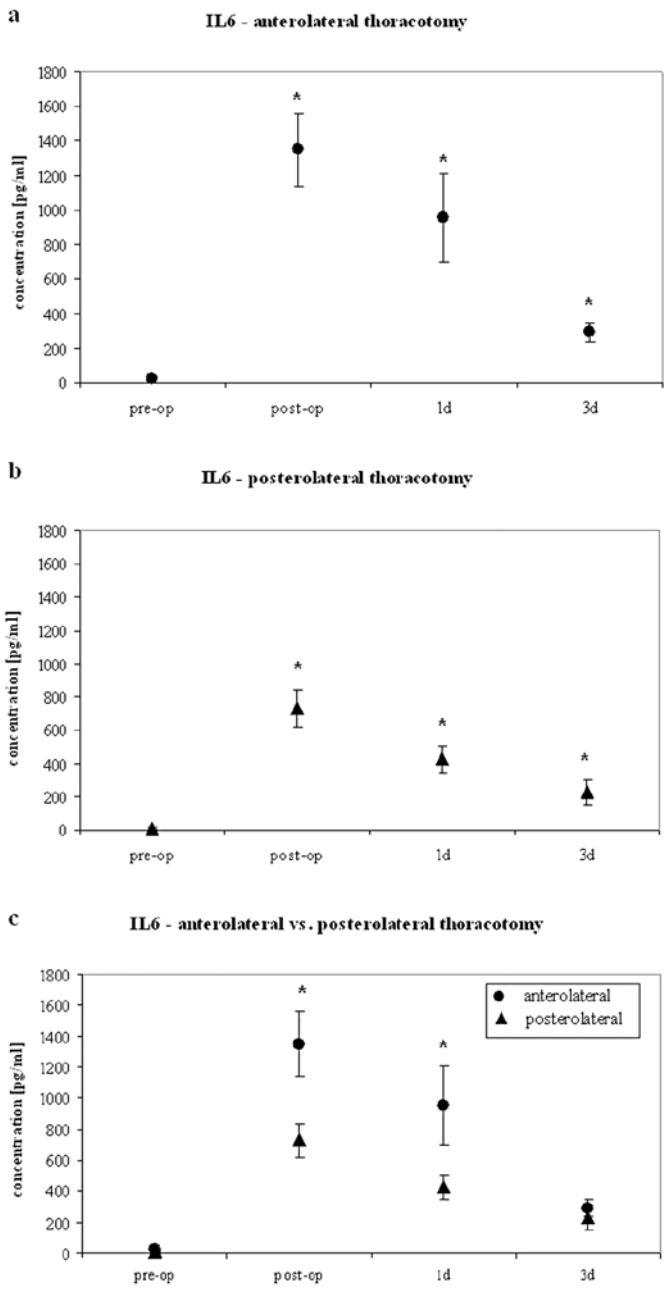

Figure 1. Concentration of serum IL6 in patients undergoing (a) anterolateral thoracotomy, (b) posterolateral thoracotomy, *p<0.05 (compared with preoperative serum levels) and (c) comparison of IL6 serum level in patients undergoing anterolateral vs. posterolateral thoracotomy, *p<0.05. Sampling points were preoperative (pre-op), postoperative (post-op) and on postoperative days 1 and 3 (d1 + d3).

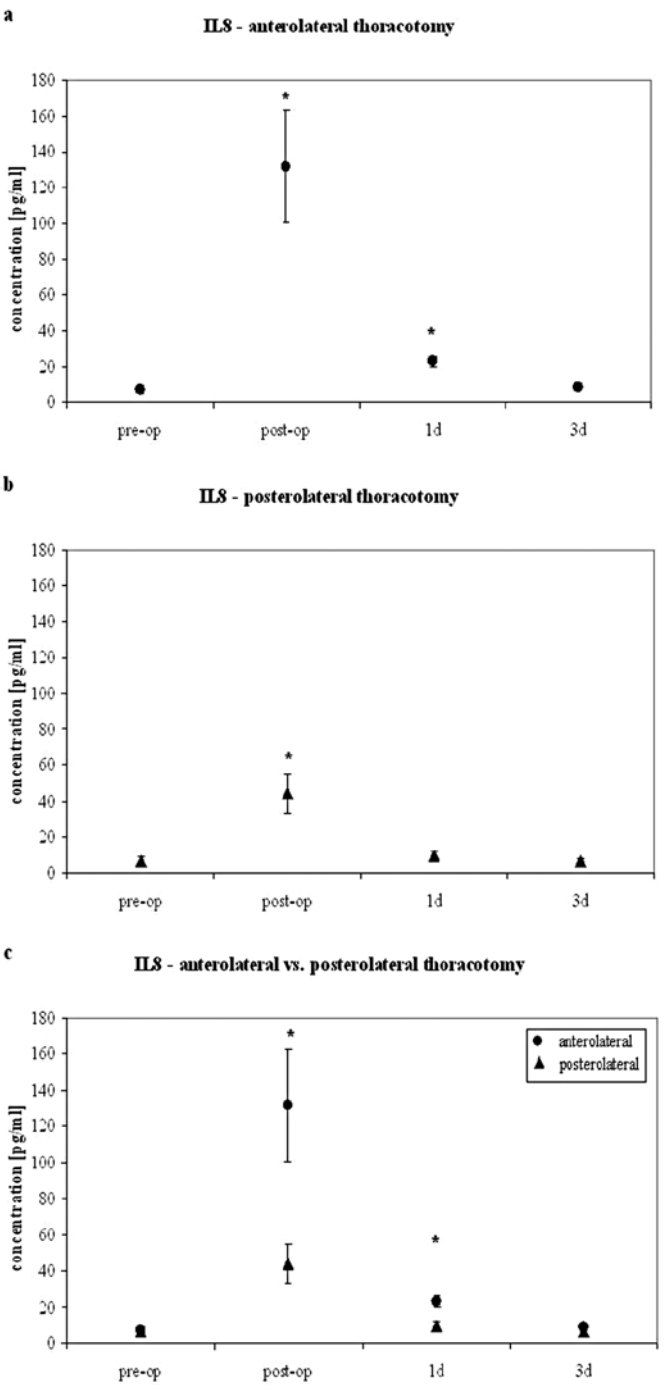

Figure 2. Concentration of serum IL8 in patients undergoing (a) anterolateral thoracotomy, (b) posterolateral thoracotomy, *p<0.05 (compared with preoperative serum levels) and (c) comparison of IL6 serum level in patients undergoing anterolateral vs. posterolateral thoracotomy, *p<0.05. Sampling points were preoperative (pre-op), postoperative (post-op) and on postoperative days 1 and 3 (d1 + d3).

the preoperative and POD3 IL6 values no differences between the two groups under investigation could be found.

Postoperative IL8 levels after anterolateral and posterolateral thoracoabdominal esophagectomy. After the anterolateral as well as the posterolateral esophagectomy, circulating IL8 was significantly increased compared to the preoperative value, peaking immediately after surgery and decreasing thereafter (Fig. 2a and b). For patients with anterolateral thorcacotomy, significantly higher levels of IL8 were observed at the end of the surgery and as well on POD1, respectively (p<0.01; Fig. 2a). In comparison, posterolateral thoracotomy patients displayed significantly higher IL8 amounts only directly after the surgery with IL8 levels declining to preoperative values already on POD1 (Fig. 2b). Comparing the two thoracotomy methods under the aspect of a putative trigger for IL8 release, we observed that patients with an anterolateral thoracotomy display significantly higher IL8 amounts at the end of the surgery (131.8±31.2 pg/ml vs. 44.0±10.9 pg/ml) as well as on POD1 (23.0±3.1 pg/ml vs. 9.7±2.3 pg/ml) when compared to the other patient group under investigation, respectively (p<0.01; Fig. 2c). In terms of the

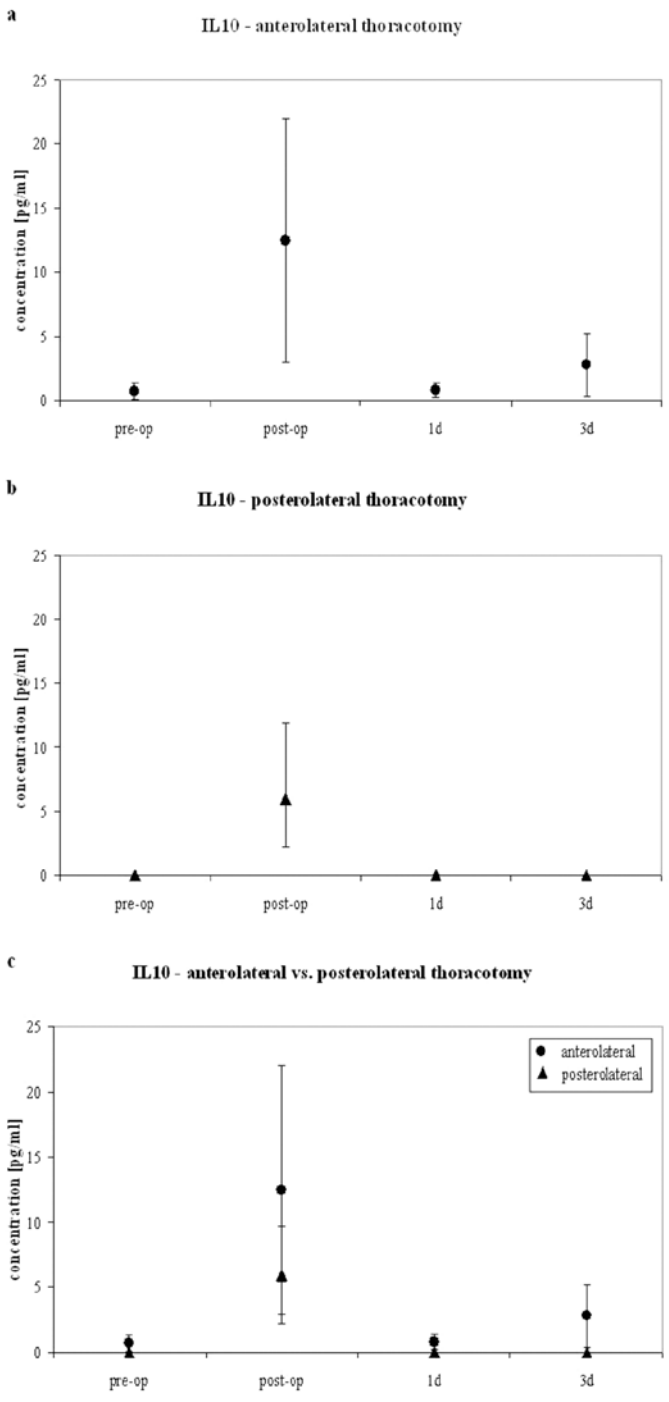

Figure 3. Concentration of serum IL10 in patients undergoing (a) anterolateral thoracotomy, (b) posterolateral thoracotomy, *p<0.05 (compared with preoperative serum levels) and (c) comparison of IL6 serum level in patients undergoing anterolateral vs. posterolateral thoracotomy, *p<0.05. Sampling points were preoperative (pre-op), postoperative (post-op) and on postoperative days 1 and 3 (d1 + d3).

preoperative and POD3 IL8 values no differences between the two groups under investigation could be found.

Postoperative IL10 levels after anterolateral and posterolateral thoracoabdominal esophagectomy. Patients with anterolateral (Fig. 3a) or posterolateral thoracotomy (Fig. 3b) show postoperative IL10 amounts which are in the range of the preoperative values. Moreover, no significant difference in IL10 serum levels were detected with regard to the respective thoracotomy method (Fig. 3c).

Discussion

In order to evaluate the potential contribution of anterolateral or posterolateral thoracotomy on the development of pulmonary complications and the degree of surgical trauma, we analyzed the serum interleukin levels of circulating IL6, IL8 and IL10 at different time points in patients who underwent an extended thoracoabdominal esophagectomy for esophageal cancer.

Severe tissue trauma, major surgery and esophageal resection in particular are pathophysiological mechanisms that may result in an excessive uncontrolled activation of inflammatory cells and mediators. This inflammatory response may play a key role in the development of cell and organ disfunction, which is the basis of ALI and ARDS (6-8). Cytokines involved in the early phase of inflammatory response include IL1, IL2, IL6 and IL8 (27-31). Some of these cytokines are produced in the lung by local resident cells such as alveolar macrophages, lung epithelial cells and fibroblasts or by cells such as neutrophils, lymphocytes, monocytes and platelets as a response to local or systemic injury (5,27,32-34).

There is strong evidence that IL6, IL8 and IL10 are useful circulating markers of the intensity of the inflammatory response in the lungs and the prognosis of patients at the onset of lung injury (35). Parsons and colleagues support the interpretation that inflammation and mechanical injury are pathophysiologically linked in the lungs, because a simple intervention, reducing tidal volume, reduced systemic inflammation and also improved outcome (35). Thus, a portion of the lung inflammatory response is likely to be a consequence of direct mechanical injury to the lung parenchyma and circulating cytokines are markers of this inflammatory response.

Various studies have reported increases in plasma cytokines and other inflammatory mediators after esophagectomy (36-41), including IL1, IL6, IL8, neutrophil elastase, soluble P- and E-selectin, thrombomodulin, tumour necrosis factor α (TNF-α) and IL10. In accordance with previous publications our study clearly shows that serum levels of IL6 and IL8 are elevated soon after major elective surgery. The innovation of our study concept addresses the question if different surgical procedures, anterolateral and posterolateral thoracotomy, respectively, have an impact on the serum cytokine levels. For the first time we have shown, that serum IL6 and IL8 concentrations were reduced to a lower level in the patient group which has undergone a posterolateral procedure.

For instance, IL6 and IL8 play important roles in the defense mechanisms that arise in response to injury. Therefore, these cytokines are considered to best reflect the magnitude of surgical stress. The factors involved in the production of these pro-inflammatory cytokines include age, stage, duration of operation, amount of intraoperative hemorrhage and area of injury (42,43). With respect to these factors, we observed no difference between the two thoracotomy groups, except for the area of lung injury. Stimulated by TNF and IL1, IL6 and IL8 are produced directly at the site of the operation injury. Subsequently, they spill over into the bloodstream (14,42,43). The apparent fact that there was a marked difference between the anterolateral and posterolateral groups in levels of IL8

can be explained by the theory that the lung is an important site of IL8 production due to ischemia/reperfusion and direct compression or crushing (44). The two procedures differ considerably in terms of the manipulation of the lungs. Thus, the lung is obtructed via spatula in the anterolateral group, whereas during posterolateral procedure the lung is passively retracted from the operation area and this difference may have been a factor in the low production of IL8 in the posterolateral thoracotomy group.

It is established that levels of circulating IL6 are well correlated with the magnitude of surgical stress, including duration of operation, blood loss and tissue damage (1-3,42). In spite of similar operation times and blood loss, higher serum IL6 concentrations were observed in patients who underwent transthoracic esophagectomy and pneumonectomy compared to patients who underwent abdominal operations such as pancreaticoduodenectomy and colorectal resection (14). These results strongly suggest that the intrathoracic procedure causes greater surgical stress to patients than abdominal procedures. After thoracic surgery, higher levels of IL6 in bronchoalveolar lavage (BAL) fluid and in fluid drained from the pleural cavity after transthoracic esophagectomy have been reported (14,39). In this study, IL6 production was observed in bronchial and alveolar epithelial cells but not in alveolar macrophages. Thus, local responses in lung tissue may be one of the sources of increases in circulating IL6 after transthoracic esophagectomy. The observed differences in serum IL6 between patients undergoing anterolateral or posterolateral thorcatomy may be explained by the circumstance that the two thoracotomy procedures under investigation differ considerably in terms of lung manipulation. Moreover, the lung tissue itself is a source for IL6.

Former studies report that the inflammatory mediators generally increase rapidly after surgery (within 6-8 h), peak by 24 h and return to baseline by 48-72 h. These findings are in part similar to our results. Thus, our patients reach peak IL6 and IL8 levels directly after surgery and IL8 returns within 72 h to baseline, whereas IL6 remains elevated. The obtained serum cytokine levels are also in accordance with previously published data (37,41). There are few studies addressing cytokine levels after esophageal resection itself. To date, most studies deal with the comparison of cytokine levels between at-risk patients for lung injury and such which had developed ALI or even ARDS in the course of their disease in order to find cytokines which predict the development of lung injury and outcome (5,45,46).

The present study of cytokine response, was intended to compare the relative traumas caused by anterolateral and posterolateral thoracotomy. We have shown that cytokines IL6 and IL8, were significantly suppressed to a lower level in patients which were subjected to a posterolateral procedure. IL6 and IL8 are key mediators in the early phase of inflammatory response and considered to best express the range of surgical stress. Therefore, our results suggest that a posterolateral thoracotomy induces a lesser vital reaction to the operation and less surgical stress.

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