World J. Surg. 22, 783–790, 1998

WORLD
Journal of
SURGERY

Serum Interleukin-6, Interleukin-8, Hepatocyte Growth Factor, and Nitric Oxide Changes during Thoracic Surgery

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Abstract. Thoracic surgery creates a different environment from abdominal surgery in respect to the surgical procedure with pulmonary collapse under unilateral ventilation. Definitive evidence whether surgical trauma during thoracotomy is involved in postoperative pulmonary infections has not been clearly demonstrated. The objectives of this study were to evaluate the influence of surgical trauma during thoracotomy on postoperative infections and to investigate the clinical significance of postoperative humoral mediators in pulmonary infections after surgery. We measured serum interleukin-6 (IL-6), IL-8, hepatocyte growth factor (HGF), and nitric oxide (NO) levels in 27 patients undergoing thoracic surgery; the measurements were before and during thoracotomy, 60 minutes after reinflation, and after surgery. The patients were divided into three groups: lobectomy patients (group A), and esophagectomy patients without (group B) or with (group C) postoperative infections. The serum IL-6 and IL-8 levels in group C were markedly elevated 60 minutes after reinflation and were significantly higher than those in group A. The serum IL-8 levels during that period in group C were significantly higher than those in group B. The postoperative serum IL-6, IL-8, HGF, and NO levels were significantly higher in group C than in group B. Taken together, intraoperative hypercytokinemia, especially IL-8, following the thoracic procedure and subsequent reinflation preceded the clinical onset of postoperative infections. Hence postoperative serum IL-6, IL-8, and HGF levels may be useful predictors of infection after esophagectomy.

Many recent studies have investigated the relation between surgical trauma and cytokine response [1–7]. Particularly, the interleukin-6 (IL-6) response to elective surgery has been characterized extensively. Many investigators reported that the peak level of serum IL-6 is correlated with surgical trauma as defined by the operating time and the volume of blood lost during surgery [3–6]. Sakamoto et al. [4] reported that the peak serum IL-6 levels in patients who underwent esophagectomy and lobectomy were significantly higher than in patients who underwent pancreaticoduodenectomy and colorectal resection, respectively, despite similar surgical trauma as defined by operating time and blood loss volume. These results indicate that thoracic surgery, such as transthoracic esophagectomy and lobectomy, may constitute severe surgical trauma unrelated to surgery time and blood loss volume. Thoracic surgery creates an environment different from that of abdominal surgery in respect to the surgical procedure with pulmonary collapse under unilateral ventilation. These observations prompted us to investigate the relevance of cytokines in regard to surgical trauma caused by thoracic surgery.

Postoperative pulmonary infections are frequently observed following transthoracic esophagectomy and in some cases develop into severe respiratory failure. This may be ascribed to the surgical trauma to the lung during thoracotomy. However, definitive evidence whether surgical trauma during thoracotomy is involved in postoperative pulmonary infections has not been clearly demonstrated. Thus, we focused on the intraoperative biologic response as well as the postoperative response.

This study was undertaken to evaluate the influence of surgical trauma during thoracotomy on postoperative pulmonary infections by measuring serum inflammatory cytokines, such as IL-6, IL-8, hepatocyte growth factor (HGF) (which has recently been noted to function as a pulmotrophic factor for regeneration of an injured lung [8–16]), and nitric oxide (NO), which is considered to be induced by proinflammatory cytokines [17, 18]. Moreover, we assessed whether these humoral mediators would be clinically useful as indicators for the prediction of postoperative pulmonary infection.

Patients and Methods

Patients

A total of 27 patients who underwent elective thoracic surgery in our hospital were included in this study. None of these patients showed any signs of preoperative complications such as diabetes, cardiopulmonary disease, or liver or renal dysfunction. The patients were divided into three groups as follows: group A, patients who underwent lobectomy (n = 12); group B, patients who underwent transthoracic subtotal esophagectomy for thoracic

This International Society of Surgery (ISS)/Société Internationale de Chirurgie (SIC) article was presented at the 37th World Congress of Surgery International Surgical Week (ISW97), Acapulco, Mexico, August 24–30, 1997.

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esophageal cancer and had no complications during the postoperative period ($n = 7$); group C, patients who underwent surgery for thoracic esophageal cancer as in group B but had postoperative pulmonary infections within a week after surgery ($n = 8$). None of the patients in group A had postoperative respiratory complications. All of the patients underwent right thoracotomy under unilateral ventilation, and the patients in groups B and C had also laparotomy with cervical anastomosis after thoracotomy. Informed consent was obtained from all patients.

Definitions and Criteria

Diagnosis of postoperative pulmonary infection was defined using the following criteria: (1) clinical auscultation positive for rales; (2) signs of lung infiltration on the chest roentgenogram; and (3) positive bacteriology of sputum. Pulmonary infections were assumed if two or three of these criteria were fulfilled.

Blood Samples

Arterial blood samples were obtained at 10 timed intervals: before surgery, 1 and 2 hours after initiation of thoracotomy, 60 minutes after reinflation of the right lung, 1 and 6 hours after surgery, and on postoperative days (PODs) 1, 3, 5, and 7. At 60 minutes after reinflation, the laparotomy had not yet been performed for esophagectomy. Blood samples were collected in pyrogen-free tubes containing ethylenediaminetetraacetic acid (EDTA) (0.34 mol/L) and were centrifuged immediately at $1000 \times g$ for 10 minutes; the resultant serum were stored at −80°C until assay was performed.

Serum IL-8 Assay

Serum IL-8 concentrations were measured by a quantitative sandwich enzyme-linked immunosorbent assay (ELISA). Anti-human IL-8 antibodies (WS-4 and A 107) and human recombinant IL-8 were kind gifts of Dr. Matsushima (University of Tokyo, Japan). Briefly, a 96-well microplate (Nunc, Roskilde, Denmark) was coated with anti-human IL-8 monoclonal antibody (WS-4: 0.5 μg/ml in 0.05 M carbonate buffer pH 9.6), 100 μl/well, and left overnight at 4°C. After washing the plate three times with phosphate-buffered saline (PBS) containing 0.05% Tween 20, unbound sites were blocked by adding 1% bovine serum albumin (BSA)-PBS, 150 μl/well, at 37°C for 1 hour. After three washes, standards and serum samples diluted in 0.5% BSA/Tween-PBS, each 100 μl/well, were added. Following overnight incubation at 4°C, the wells were washed five times with 0.05% Tween-PBS, and rabbit anti-human IL-8 antibody (A 107; 1 μg/ml in 0.5% BSA/Tween-PBS), 100 μl/well, was added as the second antibody and incubated at 37°C for 2 hours. The wells were washed five times, and alkaline phosphatase-conjugated goat anti-rabbit IgG antibody (BioSource International, Camarillo, CA, USA) diluted at 1/10,000 in 0.5% BSA/Tween-PBS, 100 μl/well, was added and incubated for an additional 2 hours at 37°C. After the final wash, enzyme substrate solution (1 mg/ml *p*-nitrophenylphosphate in 1 M diethanolamine, pH 9.8, supplemented with 0.5 mM $MgCl_2$), 100 μl/well was added and allowed to react for 30 minutes at room temperature. The enzyme reaction was stopped by the addition of 1 M NaOH. The optical density at 405 nm was then measured using an ELISA plate reader (Titertek Multiscan; Flow Laboratories, Meckenheim, Germany). All the samples were assayed at least in duplicate.

Serum IL-6 and HGF Assay

Serum IL-6 and HGF concentrations were measured using a commercially available ELISA kit (Quantikine; Research and Diagnostics Systems, Minneapolis, MN, USA) according to the protocol supplied by the manufacturer. The minimum detectable doses of the IL-6 and HGF ELISA kits were found to be 0.70 and 40 pg/ml, respectively. All the samples were assayed at least in duplicate.

Serum Nitrite/Nitrate Assay

Serum samples were filtered through an Cosmonice microfilter (pore size 0.45 μm; Millipore, Bedford, MA, USA). Serum nitric oxide (NO) was measured as nitrite/nitrate using an automated NO detector–high-performance liquid chromatography (HPLC) system (ENO-10; Eicom, Kyoto, Japan) by an HPLC-diazotization detecting method (HPLC-Griess). Briefly, serum nitrite/nitrate were separated by a reverse-phase separation column packed with polystyrene polymer (NO-PAK, 4.6×50.0 mm; Eicom), and nitrate was reduced to nitrite in a reduction column packed with copper-plated cadmium fillings (NO-RED, Eicom). Nitrite was mixed with a Griess reagent to form a purple azo dye in the reaction coil. The absorbance of the color of the product dye at 540 nm was measured by a flow-through spectrophotometer (NOD-10, Eicom). The mobile phase, which was delivered by a pump at a rate of 0.33 ml/min, was 10% methanol containing 0.15 M $NaCl/NH_4Cl$ and 4Na-EDTA 0.5 g/L. The Griess reagent, which was 0.25% HCl containing sulfanilamide 5 g/L with *N*-naphthylethylenediamine 0.25 g/L, was delivered at a rate of 0.1 ml/min. Results were plotted, and the total amount of nitrite/nitrate was determined.

Statistical Analysis

Results were expressed as the mean ± standard deviation. Statistical analysis was performed using unpaired Student's *t*-test. A p value < 0.05 was considered significant.

Results

Patient Backgrounds

There was no significant difference between group A and other two groups in terms of age, gender, preoperative respiratory function, Brinkman index, thoracic procedure time, or blood loss volume during thoracotomy (Table 1). However, the surgery time in groups B and C was significantly larger than that in group A ($p < 0.01$), and the volumes of blood loss in groups B and C were significantly larger than that in group A ($p < 0.01$). There were no significant differences between groups B and C for any of the factors.

Serial Changes of Serum IL-6

The serum IL-6 levels in groups B and C were significantly higher than those in group A from 60 minutes after reinflation until POD

Table 1. Patient backgrounds.

Parameter	Group A ($n = 12$)	Group B ($n = 7$)	Group C ($n = 8$)
Age (years)	64.4 ± 9.2	61.3 ± 12.1	62.3 ± 7.3
Gender (male/female)	10/2	6/1	6/2
Respiratory function			
%VC (%)	102.8 ± 14.0	109.4 ± 21.6	105.9 ± 20.5
$FEV_{1.0}$ (%)	74.9 ± 7.9	79.7 ± 6.2	80.2 ± 5.4
Brinkman index	935 ± 739	354 ± 413	907 ± 588
Surgery time (min)	167 ± 52	449 ± 54*	481 ± 53*
Thoracic procedure time (min)	135 ± 36	161 ± 32	169 ± 42
Total blood loss volume (ml)	268 ± 95	652 ± 212*	569 ± 246*
Blood loss volume (during thoracotomy) (ml)	246 ± 83	267 ± 39	274 ± 33

Values are the mean ± SD. VC: vital capacity; $FEV_{1.0}$: forced expiratory volume in 1 second.

*$p < 0.01$ compared to the value in group A.

7 ($p < 0.01$), except on POD 3. Comparing groups B and C, there were significant differences on PODs 1, 3, and 5 ($p < 0.05$) and POD 7 ($p < 0.01$). The intraoperative levels of serum IL-6 in groups B and C were markedly elevated at 60 minutes after reinflation, but there was no significant difference between the two groups (Fig. 1A).

Serial Changes of Serum IL-8

In all groups the serum IL-8 level reached its maximum 1 hour after surgery and then gradually declined. The serum IL-8 levels in group B and C were significantly higher than those in group A from 2 hours of thoracotomy to POD 7 ($p < 0.01$). In group C the serum IL-8 level reached a peak at 1 hour after surgery and then declined a little but remained elevated. The postoperative serum IL-8 levels in group C were significantly higher than those in group B at 1 hour after surgery, on PODs 1, 3, and 7 ($p < 0.05$), and on POD 5 ($p < 0.01$). The intraoperative levels of serum IL-8 in group C were markedly elevated at 60 minutes after reinflation, whereas those in group B gradually increased. The serum IL-8 levels at 60 minutes after reinflation were significantly higher in group C than in group B ($p < 0.01$) (Fig. 1B).

Serum IL-6 and IL-8 at 1 Hour after Reinflation

The serum IL-6 levels at 60 minutes after reinflation in groups B and C were significantly higher than that in group A ($p = 0.001$ and $p = 0.009$, respectively), but there was no significant difference between groups B and C ($p = 0.07$). On the other hand, the serum IL-8 levels in groups B and C were significantly higher than that in group A ($p = 0.0000$ and $p = 0.0002$, respectively); furthermore, the serum IL-8 level in group C was significantly higher than that in group B ($p = 0.003$) (Fig. 1C).

Serial Changes of Serum HGF

There was no significant difference in serum HGF level during surgery among the three groups. The serum HGF levels in group A demonstrated slight changes on all postoperative days, whereas those in group B gradually increased and reached the maximum on POD 1. There were significant differences between these two groups on PODs 1, 5, and 7 ($p < 0.01$) and on POD 3 ($p < 0.05$). On the other hand, the serum HGF levels in group C were markedly elevated at 1 hour after surgery and remained high up to a week after surgery. The serum HGF levels in group C were significantly higher than those in group A on all the postoperative days ($p < 0.05$) and significantly higher than those in group B from POD 1 to POD 7 ($p < 0.05$) (Fig. 2).

Serial Changes of Serum Nitrite/Nitrate

There was no significant difference among the three groups before and during surgery and 1 hour after surgery. The serum nitrite/nitrate levels in groups A and B decreased during surgery and reached a minimum 6 hours after surgery. However, these levels in group A then gradually increased, whereas those in group B remained at low levels until a week after surgery. The serum nitrite/nitrate levels in group A were significantly higher than that in group B on PODs 3, 5, and 7 ($p < 0.05$). The serum nitrite/nitrate levels in group C also decreased and reached the minimum at 1 hour after surgery but were elevated again at 6 hours after surgery and remained at high levels. The levels in group C were significantly higher than those in group A 6 hours after surgery ($p < 0.01$) and on PODs 1 and 3 ($p < 0.05$) (Fig. 3A). Furthermore, comparing groups B and C, the serum nitrite/nitrate levels in group C were significantly higher than those in group B 6 hours after surgery, on PODs 1, 3, and 5 ($p < 0.01$), and on POD 7 ($p < 0.05$) (Fig. 3B).

Discussion

In the present study we found that: (1) at 60 minutes after reinflation the serum IL-6 and IL-8 levels during esophagectomy were significantly higher than those for lobectomy; (2) especially the serum IL-8 levels at 60 minutes after reinflation were significantly higher in the patients with pulmonary infections than in those without complications; (3) postoperative serum IL-6 and IL-8 levels remained at high levels in patients with pulmonary infections; and (4) serum HGF and NO levels were markedly elevated after surgery in the patients with pulmonary infections.

Interleukin-6, which is produced by a variety of cells, including macrophages, monocytes, fibroblasts, and endothelial cells, is considered to be a useful indicator for the magnitude of surgical stress [1–7]. In our results, the peak serum IL-6 levels during esophagectomy were significantly higher than those during lobectomy. This finding may be due to the fact that transthoracic esophagectomy requires both thoracotomy and laparotomy, whereas the lobectomy requires only thoracotomy, and that the surgery time and total blood loss volume for esophagectomy are significantly higher than those for lobectomy. However, even at 60 minutes after reinflation, when the laparotomy had not yet been performed during esophagectomy, the serum IL-6 levels for esophagectomy were significantly higher than those for lobectomy, despite a similar degree of surgical trauma as defined by the thoracic procedure time and blood loss volume during thoracotomy. These findings indicate that esophagectomy may constitute severe surgical trauma during thoracotomy, unrelated to the thoracic procedure time and blood loss volume. It may be ascribed to the involvement of additional factors during the thoracic procedure. The thoracic procedure during esophagectomy consists of an extended lymphadenectomy, removal of the esophagus, and extensive manipulation and compression of the lung, as well

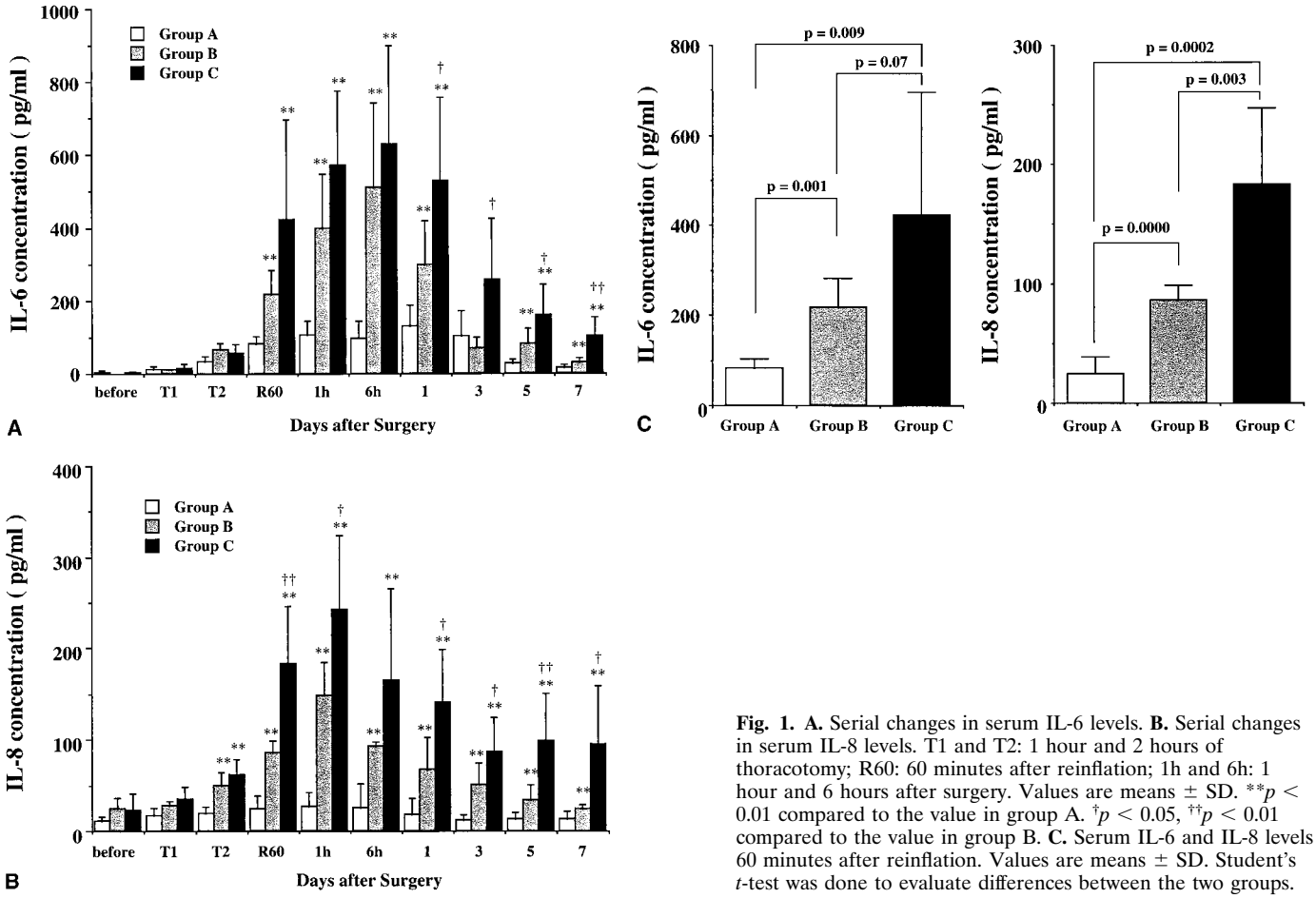

Fig. 1. A. Serial changes in serum IL-6 levels. **B.** Serial changes in serum IL-8 levels. T1 and T2: 1 hour and 2 hours of thoracotomy; R60: 60 minutes after reinflation; 1h and 6h: 1 hour and 6 hours after surgery. Values are means ± SD. $^{**}p < 0.01$ compared to the value in group A. $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$ compared to the value in group B. **C.** Serum IL-6 and IL-8 levels 60 minutes after reinflation. Values are means ± SD. Student's *t*-test was done to evaluate differences between the two groups.

as pulmonary collapse under unilateral ventilation. It is possible that these thoracic procedures caused the thoracic and pulmonary tissue damage, which in turn facilitated the induction of IL-6.

We also examined serial changes in serum IL-8, which induces neutrophil chemotaxis and degranulation of neutrophil elastase [19–22]. The serum IL-8 levels at 60 minutes after reinflation were also significantly higher with esophagectomy than with lobectomy; furthermore, there was a significant difference between the patients with and without postoperative pulmonary infections after esophagectomy. Recent studies have reported that IL-8 production may be induced by reactive oxygen metabolites generated upon reperfusion after hypoxia due to ischemia [23–27]. Sekido et al. and others [26, 27] have shown that reperfusion of ischemic lung in a rabbit model (established by occluding the left lung) caused neutrophil infiltration and destruction of pulmonary structures and local production of IL-8 in bronchoalveolar lavage fluid; moreover, the IL-8-producing cells were mainly ciliary cells of bronchiole and alveolar macrophages as revealed by immunohistologic analysis. Taking these results together, the marked elevation of serum IL-8 at 60 minutes after reinflation during esophagectomy may reflect the severe surgical stress due to reperfusion of the ischemic lung tissues, in addition to direct surgical trauma, such as manipulation and compression during the thoracic procedure. We suspect that these severe surgical stresses may contribute to the state of immunosuppression. However, no satisfactory

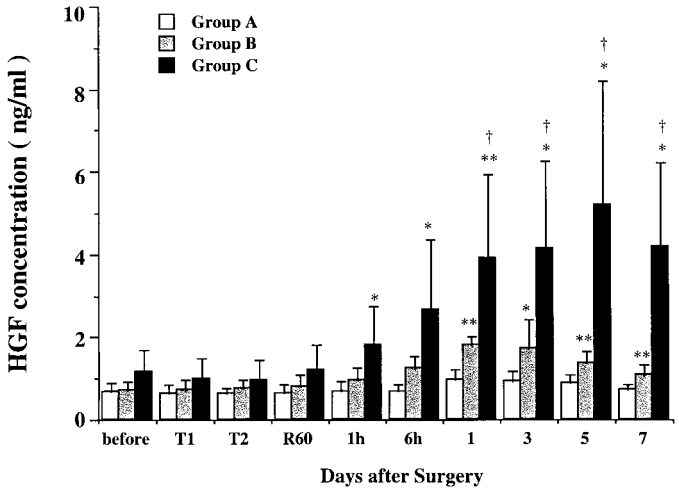

Fig. 2. Serial changes in serum HGF levels. 1h and 6h: 1 hour and 6 hours after surgery. Values are means ± SD. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to the value in group A. $^{\dagger}p < 0.05$ compared to the value in group B.

explanation has yet been found for the differences in serum IL-8 levels at 60 minutes after reinflation in esophagectomy patients with and without pulmonary infections. It may be ascribed to

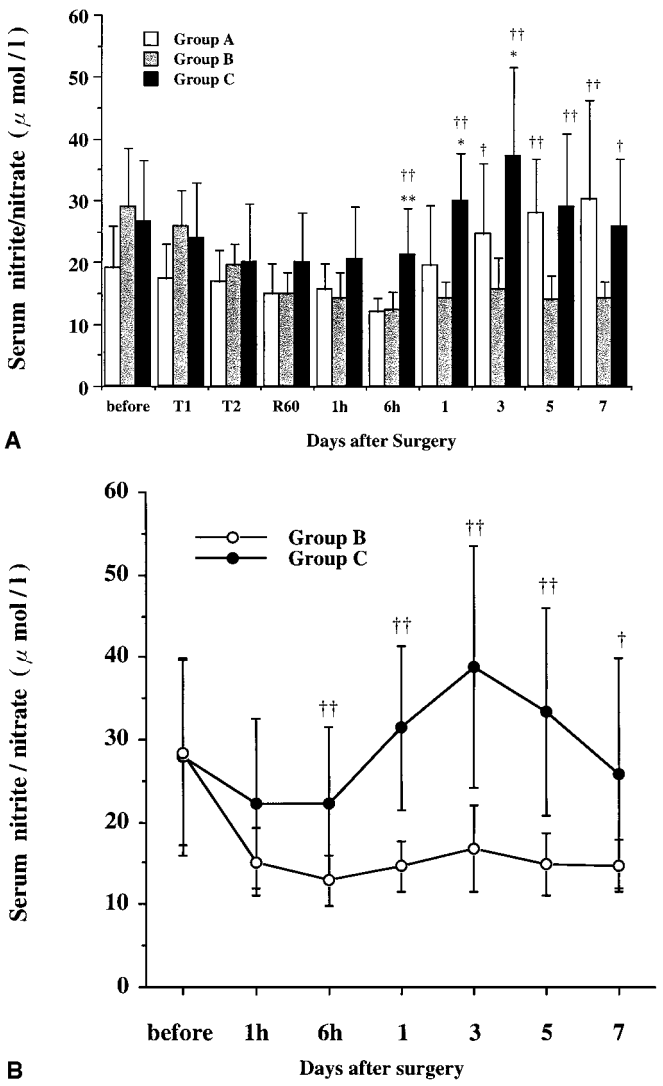

Fig. 3. A. Serial changes in serum nitrite/nitrate levels. **B.** Postoperative serial changes in serum nitrite/nitrate levels after esophagectomy. 1h and 6h: 1 hour and 6 hours after surgery. Values are means ± SD. $^{*}p < 0.05$, $^{**}p < 0.01$ compared to the value in group A; $^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.01$ compared to the value in group B.

immunologic susceptibility of individuals to surgical trauma or to the involvement of other factors in the injury. Further investigation is needed to clarify this mechanism.

Hepatocyte growth factor was originally considered to be a potent hepatotrophic factor for liver regeneration [28–30]. However, recently it has been noted to function as a pulmotrophic factor for regeneration of injured lung [8–16]. Our results show that serum HGF levels after esophagectomy were markedly elevated in patients with postoperative pulmonary infections when compared to that in patients without complications. Yanagita et al. [8] reported that the serum HGF concentration in patients with various lung diseases is much higher than that in healthy donors. Moreover, Maeda et al. [9] have revealed that the serum HGF levels in surviving patients with inflammatory lung disease rapidly decrease with treatment but not in the patients who ultimately died. These results suggest that serum HGF levels may be a useful indicator for predicting pulmonary infections and prognosis in those with inflammatory lung disease. The major sources of HGF in the lung are mesenchymal cells, such as macrophages, fibroblasts, and endothelial cells [10, 11]. It is possible that activating these cells in inflammatory lung produces HGF. In injured lung, bronchial and alveolar type II epithelium replication are essential for tissue repair and lung regeneration [12]. HGF stimulates the proliferation of these epithelial cells [13–16]. In this context, HGF may play an important role in bronchial and alveolar type II epithelium replication in inflammatory lung. Moreover, our data showed that the postoperative serum HGF levels in esophagectomy patients without complications were significantly higher than those in lobectomy patients from the first postoperative day. This result suggests that serum HGF levels reflect the severity of lung injury caused by surgical trauma as well as by pulmonary infections. Whether organs other than the lung produce HGF remains elusive. More in vitro and in vivo investigations are needed to clarify the clinical and biologic significance of HGF in inflammatory lung and lung injury after surgery.

Many studies have investigated the clinical relevance of NO production in various inflammatory lung diseases, such as asthma [31], upper respiratory tract infections [32], and acute lung allograft rejection [33]. NO is a potent free radical synthesized from L-arginine by the NO synthases (NOS), which exist in three isoforms. Constitutive forms (cNOS) are present in endothelial cells and neurons; another isoform (iNOS) is induced by proinflammatory cytokines such as IL-1 and tumor necrosis factor α (TNFα), endotoxin, or oxidants [17, 18]. iNOS can be induced in the lung by a variety of inflammatory cells including macrophages and neutrophils as well as in endothelial and epithelial cells [17, 31–33]. Our results suggest that the increased concentrations of serum nitrite/nitrate in patients with pulmonary infections may be induced by activation of these cells in the inflammatory lung.

There is no satisfactory explanation for the postoperative elevation of serum nitrite/nitrate levels in lobectomy patients and the prolonged low levels in esophagectomy patients despite the lack of postoperative pulmonary infections in either group. Perhaps it can be ascribed to the exogenous nitrite/nitrate present in the diet. Indeed, lobectomy patients are on an oral diet usually the day after surgery that contains a large amount of nitrite/nitrate [34], whereas the esophagectomy patients are administered intravenous infusions for long periods. This study demonstrated that serum nitrite/nitrate levels in all patients gradually decreased during surgery, a tendency that continued until the early phase after surgery. It is conceivable that the metabolism of NO in surgical stress may be involved in this phenomenon, although no definitive evidence could be obtained by indirect measurement of NO as its stable end-products, nitrite and nitrate.

It is difficult to evaluate the clinical significance of serum NO changes during thoracic surgery because the pathophysiologic role of NO has long been controversial. NO has been documented to attenuate neutrophil-mediated oxidative stress by interacting with the superoxide-producing enzyme NADPH oxidase [35]. On the other hand, some investigators have postulated that NO and superoxide (O_2^-) combine to form peroxynitrite ($ONOO^-$), which induces some oxidative stress such as lipid peroxidation [36] and nitrosolization of proteins [37] and as a consequence causes extensive cell damage [38]. As for the estimation of nitrosolization of protein, 3-nitrotyrosine produced by reaction of NO with the tyrosine residue can be identified in biologic samples using the

highly sensitive HPLC with electrochemical detection [39]. Further studies concerning these oxidative stresses and nitrite/nitrate are needed to clarify the clinical significance and pathophysiologic mechanism of NO during surgical trauma and infection after thoracic surgery.

It is possible that the elevation of cytokines and growth factor during surgery and the early postoperative period in this study is associated with postoperative pulmonary infections. However, there was no pathophysiologic evidence whether this early change is cause or effect for those patients who go on to develop pulmonary complications. Moreover, it is difficult to assess whether the host biologic responses reflect injury or inflammation because of the complex cascade and counterregulatory mechanism of cytokines [1–3]. Thus there may be some other factors up-regulating these cytokines and growth factor that are associated with infection. Alternatively, the elevations of these humoral mediators may be due to down-regulation of some suppressive factors, such as soluble TNF receptor, IL-1 receptor antagonist, IL-4, and IL-10 [2]. Proinflammatory cytokines, IL-1 and TNFα are considered to induce the production of IL-6 and IL-8 [3, 20].

Baigrie et al. [7] reported that the IL-1β response to major surgery (e.g., aortic surgery) was detected only by intensive sampling during the perioperative period, and that the rise of IL-1β preceded the IL-6 response by several hours. Furthermore, the rise in IL-6 levels has been demonstrated to precede the C-reactive protein response [1–7], which is consistent with the evidence that IL-1β and IL-6 are mediators of acute-phase proteins [40]. One of the antiinflammatory cytokines, IL-4, has been shown to reduce the production of TNFα in interferon gamma (IFNγ)-stimulated macrophages and to reduce production of IL-1 and prostaglandin E_2 [41]. IL-10 also suppresses the production of a series of macrophage cytokines, including TNFα, IL-1α, IL-1β, IL-6, and IL-8 [42, 43]. Hensler et al. [44] demonstrated that major surgery results in a severe defect of T lymphocyte proliferation and cytokine secretion, and that the production of IL-2, IFNγ, TNFα, and IL-4 (but not IL-10) decreases during the early postoperative course, whereas production of IL-10 increases late after surgery. The correlation between the early elevation of the humoral mediators in our study and these antiinflammatory cytokine levels during surgery is not clear. Further studies on antiinflammatory and inflammatory cytokines are needed to clarify the pathophysiologic and immunologic mechanisms of pulmonary infections after thoracic surgery.

Conclusions

Serum IL-6 levels may reflect the magnitude of direct tissue injury by thoracic procedures. Intraoperative hypercytokinemia, especially IL-8, following the thoracic procedure and subsequent reinflation preceded the clinical onset of postoperative pulmonary infections. These findings raise the possibility that blocking the intraoperative hypercytokinemia may be beneficial for patients with pulmonary infections after surgery. Moreover, postoperative serum IL-6, IL-8, and HGF levels may be useful indicators for predicting pulmonary infection after esophagectomy. In addition, HGF may play an important role in lung regeneration in inflammatory lung and injured lung. No definite conclusion was reached concerning the clinical significance of serum nitrite/nitrate levels during surgical trauma and postoperative infection after thoracic surgery. We recommend routine measurement of serum IL-6, IL-8, and HGF to identify patients who will develop pulmonary complications after stressful surgery such as esophagectomy and lung transplantation.

Résumé

La chirurgie thoracique diffère de la chirurgie abdominale par la nécessité d'obtention une exclusion pulmonaire unilatérale. Cependant, le rôle de l'agression chirurgicale dans les infections pulmonaires postopératoires n'est pas clairement démontré. Les buts de cette étude ont été d'une part d'évaluer l'influence du traumatisme chirurgical sur la survenue des infections pulmonaires pendant la thoracotomie et d'autre part d'évaluer la signification clinique des médiateurs humoraux postopératoires dans l'infection pulmonaire. Nous avons mesuré l'interleukine-6 (IL-6), l'interleukine 8 (IL-8), le facteur de croissance des hépatocytes (HGF) et l'oxyde nitrique (NO) chez 27 patients ayant une chirurgie thoracique, avant, pendant, 60 min après ré-expansion pulmonaire et après l'acte chirurgical. On a divisé les patients en trois groupes: lobectomie (groupe A) et oesophagectomie sans ou avec infection postopératoire (groupes B et C, respectivement). Les taux d'IL-6 et d'IL-8 dans le sérum étaient très élevés dans le groupe C à 60 min après la réexpansion, et ces taux étaient significativement plus élevés que dans le groupe A. Les taux d'IL-8 sériques dans le groupe C pendant cette période étaient significativement plus élevés que dans le groupe B. Les taux d'IL-6, d'IL-8, de HGF et de NO étaient significativement plus élevés dans le groupe C que dans le groupe B. Ensemble, l'hypercytokinémie peropératoire, surtout l'IL-8, après une intervention thoracique et la ré-expansion, précédaient le début clinique des infections postopératoires. En conclusion, les taux d'IL-6, d'IL-8 et de HGF en postopératoire peuvent être utilisés comme prédicteurs d'infection après l'oesophagectomie.

Resumen

La cirugía torácica crea condiciones intraoperatorias diferentes a las de la cirugía abdominal, principalmente relativas al colapso pulmonar bajo ventilación unilateral. No existe evidencia definitiva que compruebe el efecto del trauma de la toracotomía sobre el desarrollo de infecciones pulmonares postoperatorias. El propósito del presente estudio fue el de evaluar la influencia del trauma quirúrgico que ocurre durante la toracotomía sobre las infecciones postoperatorias, e investigar la significación clínica de los mediadores humorales postoperatorio en las infecciones pulmonares que aparecen después de la cirugía. Se efectuó la determinación de los niveles séricos de interleucina 6 (IL-6), interleucina 8 (IL-8), factor de crecimiento del hepatocito (hepatocyte growth factor, HGF) y óxido nítrico (ON) en 27 pacientes sometidos a cirugía torácica, antes y durante la toracotomía, y a los 60 minutos luego de la re-expansión pulmonar y después de la cirugía. Los pacientes fueron divididos en tres grupos: los pacientes sometidos a lobectomía (grupo A), los sometidos a esofagectomía sin o con infecciones postoperatorias (grupos B y C, respectivamente). Los niveles séricos de IL-6 e IL-8 en el grupo C aparecieron marcadamente elevados a los 60 minutos luego de la reexpansión, a la vez que significativamente más altos que en el grupo A. Los niveles de IL-8 en el mismo período aparecieron mucho más altos que en el grupo B. Los niveles séricos postoperatorios de IL-6, IL-8, HGF y ON aparecieron significativamente

más altos en el grupo C que en el B. De lo anterior, se ve que la hipercitocinemia intraoperatoria, especialmente de IL-8, luego de un procedimiento quirúrgico y la subsiguiente re-expansión pulmonar, precede al comienzo clínico de las infecciones pulmonares postoperatorias y los niveles postoperatorios de IL-6, IL-8, HGF, pueden ser indicadores de predicción del desarrollo de infecciones después de una esofagectomía.

Acknowledgments

The authors thank Drs. Kunimoto Nezu, Hiroaki Nishioka, and Soichiro Kitamura for kindly providing blood samples. This work was supported in part by a Research Grant-in Aid from the Ministry of Education, Science, and Culture of Japan (B-08457330).

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Invited Commentary

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The purpose of this report is to further catalog the cytokines, growth factor, and nitric oxide as markers of surgical trauma or postoperative complications. There is no question that it is important for surgeons to understand the importance of cytokines as critical determinants of the response to injury and infection.

Although it was originally thought that cytokines primarily influenced immunologic homeostasis, it has now been shown that the situation is far more complex and that they also have an influence on cardiovascular and metabolic functions. Furthermore, it is appreciated that the activation of cytokines is complex and that the up-regulation and down-regulation of these small proteins are under the influence of many factors, both intracellularly and extracellularly.

One of the positive features of this report is that the authors have studied two of the cytokines (IL-6 and IL-8) in human disease. Unfortunately, the patients are somewhat heterogeneous, which complicates interpretation of the data. The authors have shown that IL-6 levels are significantly higher in their groups B (esophagectomy without complications) and C (esophagectomy with complications) than in group A (lobectomy). There were also significant differences within groups B and C. Does this reflect the amount of surgical injury, the additive insult of infection, or both? Similarly, IL-8 was significantly higher in group B and C patients compared to group A patients. Hepatic growth factor was also increased in groups B and C compared to that in group A. The authors conclude that subtotal esophagectomy and the addition of infection results in more surgical trauma and elaboration of cytokines than simple lobectomy. Intuitively, this seems right, but we must be careful about overinterpreting the results or ascribing cause and effect. We certainly must be careful and constrained when attempting to manipulate the cytokine system with therapeutic intervention, such as monoclonal antibody therapy. Cytokines are not all good, nor are they all bad. They are simply messengers in a complex inflammatory cascade that has profound effects on other metabolic functions.

Similarly, we must be careful when interpreting any data on nitric oxide (NO) metabolism. NO has multiple functions including vasodilatory, neurotransmitter, and bactericidal properties. NO metabolism is further complicated in that it is difficult to measure the active by-products. NO quickly combines with proteins (nitrosolization) or with superoxide to perform perioxynitrate, which may be even more toxic than NO. These substances were not measured. The serum nitrite/nitrate assay is a crude estimate of NO metabolism. Although the authors show mixed results with their nitrite/nitrate assay, they conclude that in 6 hours the levels in group C were significantly higher than those in group A. One must be careful when reaching conclusions based on this information. Did this NO come from the macrophage, the endothelial cell, or some other yet undefined tissue? Does the elevation of NO at 6 hours define a group of patients who will develop a pulmonary infection? Probably not.

Cytokine and NO metabolic events are exciting areas of research. Our understanding of both of these important control mechanisms are primitive at best. We must be circumspect when interpreting the information provided in human studies such as this one. Finally, we must be careful not to initiate prematurely the therapeutic blockade of some cytokines or NO prior to fully understanding all of the feedback mechanisms and the genetic controls of these compounds.