Acta Medica et Biologica
Vol. 45, No. 1, 1-5, 1997

Influence of Operative Injury on the Systemic Inflammatory Response Syndrome in Esophageal Cancer Surgery

Nobuaki SATO, Akira OHKAWA, Manabu OYAMATSU, Yu KOYAMA, Seiji KAYAMA, Mitsuhiro HAYASHI, Tomoi SATO and Katsuyoshi HATAKEYAMA

The First Department of Surgery, Niigata University School of Medicine, Niigata, Japan

Received February 7 1997; accepted March 14 1997

Summary. **Background: The systemic inflammatory response syndrome (SIRS) occurs after a wide variety of insults. Recent studies have revealed that the number of SIRS criteria exhibited by a patient may have clinical importance. For this reason, we sought to determine whether the magnitude of a surgical insult is associated with the number of SIRS criteria satisfied.**
Study design: We retrospectively investigated relationships between the number of SIRS criteria and the type of surgical procedure, either transthoracic (n=79) or transhiatal esophagectomy (n=42), in 121 consecutive male patients younger than 75 years of age with carcinoma of the esophagus.
Results: Operative injury was more extensive in the transthoracic group than in the transhiatal group in terms of the mean operative time (392 ± 65 versus 215 ± 70 min, $p<0.0001$) and estimated intraoperative blood loss (693±309 versus 436±316 mL, $p<0.0001$). Prevalence of SIRS did not differ between the two groups. Pyrexia was more frequent in the transthoracic group than in the transhiatal group ($p=0.004$). Conversely, tachypnea was commoner in the transhiatal than in the transthoracic group ($p=0.0039$). The mean number of SIRS criteria exhibited was the same, 2.1±0.9 in the transhiatal group and 2.3±0.7 in the transthoracic group.
Conclusion: There was no difference in the mean number of SIRS criteria exhibited following either transthoracic or transhiatal esophagectomy for carcinoma of the esophagus, even though the magnitude of the operative injury was greater in patients undergoing transthoracic esophagectomy in terms of operative time and estimated blood loss. Our results show more a frequent occurrence of fever in the transthoracic group and a higher rate of tachypnea in the transhiatal group, a pattern possibly reflecting mechanical ventilation of the transthoracic patients.

Correspondence: Nobuaki Sato, M.D. The First Department of Surgery, Niigata University School of Medicine, 1-757 Asahimachi-dori, Niigata 951, Japan.

Key words—systemic inflammatory response syndrome (SIRS), magnitude of operative injury, esophageal cancer, transhiatal esophagectomy, transthoracic esophagectomy, mechanical ventilator support.

INTRODUCTION

The term systemic inflammatory response syndrome (SIRS) was proposed to describe "any inflammatory process independent of its cause as can be seen after a wide variety of insults".[1] Members of the consensus conference stated that "further work is needed to characterize the clinical and prognostic importance of the proposed syndromes". It has been reported that almost any patient in the surgical intensive care unit (SICU) exhibits SIRS.[2] Therefore, because of its poor specificity, SIRS was not thought to be helpful in predicting severe sepsis and septic shock.[2]

However, a recent study has revealed that the number of SIRS criteria that the patients display may clinical importance of the syndrome.[3] Patients with two SIRS criteria had twice rate of death (7%) as those who never developed SIRS (3%).[3] Patients with more than two criteria for SIRS were more likely to develop sepsis rapidly with higher rates of organ dysfunction and higher mortality rates (10%).[3] SIRS with only two criteria—as initially proposed—is less helpful in defining a subset of ICU and ward patients who are at especially high risk for the development of sepsis than patients with SIRS with three or all four of the criteria.[3] Jones has shown that the crude mortality rate at 28 days increased sequentially as more SIRS criteria were exhibited, rising from 12% in non-SIRS bacteremia to 36% when all four criteria were exhibited in bacteremic general medical patients.[4]

The systemic inflammatory response syndrome is an inflammatory reaction resulting from systemic mediators i.e., cytokines. Three of the most important cytokines are tumor necrosis factor, interleukin (IL)-1, and IL-6.[5] In burns, the extent of the increase in IL-6 concentration correlates directly with the extent of burn injury.[6] It also has been shown that the increased IL-8 concentration correlates with the extent of injury expressed by burn size.[7] However, few studies have evaluated the clinical importance of SIRS as it relates to the magnitude of the surgical insult in postoperative patients with cancer. The degree and duration of early SIRS depends on the initial insult,[8] and the plasma IL-6 concentration may serve as an indicator of the magnitude of a surgical insult.[9] Our hypothesis was that the magnitude of a surgical insult is associated with the number of SIRS criteria. We investigated the relationships between the number of SIRS criteria that the patients displayed and the type of surgical procedure performed in patients with carcinoma of the esophagus.

MATERIALS AND METHODS

Patients

We retrospectively evaluated 121 consecutive male patients with carcinoma of the esophagus younger than 75 years of age from January 1990 to December 1994. All patients were required to be able to carry on normal activity or to be ambulatory in spite of their symptoms (Eastern Cooperative Oncology Group performance status of 0-1).

Either transthoracic or transhiatal esophagectomy was chosen to investigate the relationships between the number of SIRS criteria that the patients experienced and the type of surgical procedure performed in this study.

Transthoracic esophagectomy with lymphadenectomies was performed on patients with a good performance status who were predicted to have tumor invasion of the submucosa with a lesion amenable to curative resection. Transhiatal esophagectomy was performed on patients who had early mucosal tumors, extensive disease beyond the scope of curative resection, or impaired physical functioning.

Transthoracic esophagectomy with lymphadenectomies was performed using a three-phase approach with nodal clearance in the neck, mediastinum, and abdomen. Initially, the patient underwent a synchronous laparotomy and neck exploration. An abdominal lymph node dissection was performed in the epigastric region and along the left gastric, common hepatic, and celiac arteries. A gastric tube (n=70) or the colon (n=9) was used as an esophageal substitute with the anastomosis in the neck. Following this the abdominal and cervical incisions were closed, the patient was turned onto his left side, and a standard posterolateral right thoracotomy was performed for removal of the thoracic esophagus.

Transhiatal esophagectomy without thoracotomy was performed through the thoracic inlet and the hiatus with limited abdominal lymphadenectomy.[10] Cervical esophagointestinal continuity was restored with either a gastric tube (n=37) or a colonic segment (n=5) in the transhiatal group.

One hundred nineteen carcinomas were classified histologically as squamous cells. Two were classified histologically as adenocarcinoma. Seven of 121 patients were administered with 5-fluorouracil by continuous infusion and cisplatin by bolus preoperatively to improve tumor control (n=2 in the transthoracic group, n=5 in the transhiatal group).

The general management of the patients undergoing esophagectomy included postoperative analgesia, epidural block, and the provision of intravenous colloids. Intravenous colloid solutions were administered intra-and postoperatively to avoid the accumulation of interstitial pulmonary fluids. The patients who underwent transthoracic esophagectomy were intubated and mechanically ventilated under varying conditions of intermittent mandatory ventilation, using the Siemens 900B or C Servo-Ventilator (Siemens-ELEMA AB., Sweden). The initial setting for the ventilator included 10 mL/kg of tidal volume at a rate of 15 breaths/min with a fractional concentration of oxygen of 0.4.[11]

Postoperative pneumonia was diagnosed by a persistent infiltrate on chest roentgenograms, fever (temperature greater than 38°C), and a peripheral leukocytosis.

Definition of SIRS

The definition for SIRS was first reported by the American College of Chest Physicians-Society of Critical Care Medicine Consensus Conference.[1] SIRS was defined as a condition including two or more of the following: 1) temperature greater than 38°C or less than 36°C; 2) heart rate greater than 90 beats per min; 3) respiratory rate greater then 20 breaths per min or $PaCO_2$ less than 32 torr (<4.3 Kpa); 4) white blood cell count greater than 12000 or less than 4000 cells/mm^3, or including more than 10% bands. However, we did not measure the percentage of immature forms of white blood cells. Therefore, the definition for SIRS we used in this particular study did not

include an increase in immature forms of white blood cells. We collected data during a 72-hour period following surgery to evaluate the effect of the magnitude of the surgical insult on the development of SIRS, since it has been shown that a majority of patients develop SIRS within 48 h following surgery.[2] Most infectious complications occurred at least 5 days after the operation and were not thought to play a role in the development of SIRS during the 72-hour period following esophagectomy.

Statistics

Data are presented as the mean ± standard deviation. Mann-Whitney's U test was used for comparing patient details. A chi-square test was used to examine differences in proportions between patient groups. A p value of less than 0.05 was considered significant. All statistical analyses were carried out using StatView 4.1 for Macintosh.

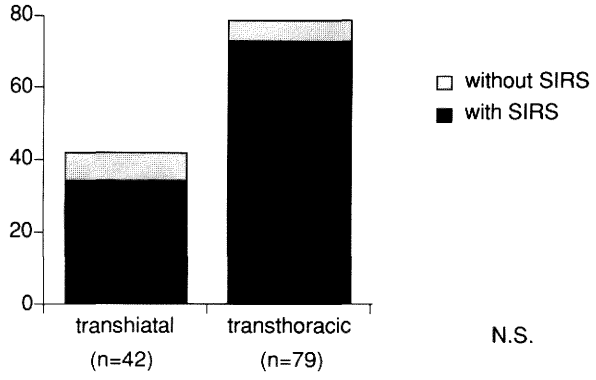

Fig. 1. Prevalence of the systemic inflammatory response syndrome.
N.S.: not significant.

RESULTS

The patients' characteristics are shown in Table 1. A residual tumor was found in 19 patients in the transhiatal group, whereas 9 of the 79 patients had a residual tumor in the transthoracic group following esophagectomy ($p<0.0001$). Significant differences in the operative time ($p<0.0001$) and blood loss ($p<0.0001$) were found between both groups. The number of patients who required mechanical ventilation was significantly greater in the transthoracic esophagectomy group ($p<0.0001$). Eight (10%) of 79 patients in the transthoracic group developed postoperative pneumonia compared to 1 (2.4%) of 42 patients in the transhiatal group. None of the patients who received preoperative chemotherapy developed postoperative pneumonia.

No difference was found in prevalence of SIRS between the two groups (Fig. 1). The number of SIRS criteria was 2.1 ± 0.9 in the transhiatal group and 2.3 ± 0.7 in the transthoracic group. Table 2 illustrates the relationship between the SIRS criteria and the operative procedure. The incidence of tempera-

Table 1. Patient characteristics

	Transhiatal (n=42)	Transthoracic (n=79)	P value
Age (yrs)	63.6±6.4	62.3±5.9	0.149
%Uswt (%)	95±7	96±5	0.61
Operation time (min)	215±70	392±65	<0.0001
Blood loss (g)	436±316	693±309	<0.0001
Mechanical ventilation	4(10%)	76(96%)	<0.0001
Postoperative pneumonia	1(2.4%)	8(10%)	<0.1

Data are presented as the mean±SD
%Uswt: body weight expressed as a percentage of usual weight

Table 2. Clinical manifestations and operative procedure

	Transhiatal (n=42)	Transthoracic (n=79)	P value
Temperature>38°C or <36°C	29(69%)	71(90%)	0.004
Heart rate>90 beats/min	29(69%)	64(81%)	0.14
Respiratory rate>20 breaths/min or $Paco_2$ <32 torr	19(45%)	16(20%)	0.0039
White blood cell count>12,000×10^6/L or <4,000×10^6/L	12(29%)	29(37%)	0.37

ture change was higher in the transthoracic esophagectomy group compared to that in the transhiatal group ($p=0.004$). However, the number of patients with tachypnea was higher in the transhiatal group than in the transthoracic group ($p=0.0039$). There were no significant differences in the rates of tachycardia and white blood cells counts between the groups.

DISCUSSION

Most patients undergoing esophagectomy for carcinoma of the esophagus developed SIRS. In our study there was no difference in the prevalence of SIRS following either transthoracic or transhiatal esophagectomy for carcinoma of the esophagus, even though the magnitude of the operative injury was greater in patients undergoing transthoracic esophagectomy in terms of operative time and estimated blood loss. There was no significant difference between the groups in the number of SIRS criteria exhibited by the patients.

Previously we have shown that energy expenditure following transhiatal esophagectomy is lower than that after transthoracic esophagectomy; this is a result of reduced surgical stress.[13] We expected a higher rate of SIRS in patients undergoing transthoracic esophagectomy. It is likely that prophylactic postoperative mechanical ventilator support prevented the development of tachypnea in patients undergoing transthoracic esophagectomy. The patients on mechancical ventilation were sedated routinely, and some received neuromusclar blocking agents. The ventilatory support and lack of respiratory distress may also have prevented the development of tachycardia.

It is plausible that prophylactic mechanical ventilatory support makes it less likely to find a true difference in the number of SIRS criteria shown by the patients between the transthoracic and transhiatal esophagectomies than it would be under comparable general management following different operative procedure. It has been reported that transthoracic esophagectomy with extended lymph node dissection results in a reduction of plasma colloid osmotic pressure (COP) with a diminution of the COP-pulmonary artery wedge pressure gradient and resultant pulmonary edema.[12] Thus we used prophylactic mechanical ventilatory support and intravenous colloids early in the postoperative period following transthoracic esophagectomy.

Our results show that the number of SIRS criteria displayed by the patients was the same between the groups, in addition to a more frequent occurrence of fever in the transthoracic group and a higher rate of tachypnea in the transhiatal group, a pattern possibly reflecting mechanical ventilation of the transthoracic patients. The likelihood that prophylactic postoperative mechanical ventilator support prevented the development of tachypnea must be considered in patients undergoing transthoracic esophagectomy. Assuming that prophylactic postoperative ventilatory support is not applied to the patients following transthoracic esophagectomy, it is possible that tachypnea could develop which makes the number of SIRS criteria exhibited by the patients in the transthoracic group increase significantly than that in the transhiatal group. Further studies are needed to determine if the magnitude of the surgical insult has a significant influence on the number of SIRS criteria that patients exhibit under comparable general management following different operative procedures. It will be important to match patients according to the degree of ventilatory support and sedation or paralysis.

REFERENCES

1) American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* **20:** 864-874, 1992.
2) Pittet D, Rangel-Frausto S, Li N, Tarara D, Costigan M, Rempe L, Jebson P, Wenzel RP: Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. *Intensive Care Med* **21:** 302-309, 1995.
3) Rangel-Frausto S, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP: The natural history of the systemic inflammatory response syndrome (SIRS)—A prospective study. *JAMA* **273:** 117-123, 1995.
4) Jones GR, Lowes JA: The systemic inflammatory response syndrome as a predictor of bacteraemia and outcome from sepsis. *Q J Med* **89:** 515-522, 1996.
5) Bone RC: Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation. [Review] *Crit Care Med* **24:** 163-172, 1996.
6) Schluter B, Konig B, Bergmann U, Muller FE, Konig W: Interleukin 6-A potential mediator of lethal sepsis after major thermal trauma: evidence for increased IL-6 production by peripheral blood mononuclear cells. *J Trauma* **31:** 1663-1670, 1991.
7) Vindenes H, Ulvestad E, Bjerknes R: Increased levels of circulating interleukin-8 in patients with

large burns: relation to burn size and sepsis. *J Trauma* **39:** 635-640, 1995.
8) Sauaia A, Moore FA, Moore EE, Lenzotte DC: Early risk factors for postinjury multiple organ failure. *World J Surg* **20:** 392-400, 1996.
9) Parry-Billings M, Baigrie RJ, Lamont PM, Morris PJ, Newsholme EA: Effects of major and minor surgery on plasma glutamine and cytokine levels. *Arch Surg* **127:** 1237-1240, 1992.
10) Nishimaki T, Suzuki T, Tanaka Y, Aizawa K, Hatakeyama K, Muto T: Intramural metastases from thoracic esophageal cancer: local indicators of advanced disease. *World J Surg* **20:** 32-37, 1996.
11) Ohtani H: Studies on respiratory and hemodynamic changes in one-stage operation for esophageal cancer surgery-with special emphasis on surgical procedures in relation to surgical influences. *J Jp Assoc Thorac Surg* **32:** 1123-1142, 1984.
12) Sato N, Kusama A, Ohkawa A, Koyama Y, Oyamatsu M, Kayama S, Yoshikawa K, Tanaka O, Muto T: Resting energy expenditure in patients undergoing transhiatal or transthoracic esophagectomy for carcinoma of the thoracic esophagus. *Br J Surg* **80:** 1413-1415, 1993.