厚生労働科学研究費補助金（医療技術評価総合研究事業）
平成18年度　分担研究報告書
日米のSSI発生率の比較に関する研究

分担研究者　針原康　NTT東日本関東病院　手術部長

研究要旨

SSI発生率に関して、本邦のJNISデータ、米国のNNISデータおよびエビデンスレベルの高い雑誌に掲載された論文でのSSI発生率を検討し、日米のSSI発生率の比較を試みた。

NNISのデータでは、論文に報告された値やJNISのデータに比較して、SSI発生率がかなり低値であり、その精度に問題があると思われた。NNISデータの精度の問題から、日米のSSI発生率を単純に比較することは困難であったが、日本のSSI発生率が米国と比較して特に高いとは考えられなかった。

A. 研究目的

SSI（手術部位感染、Surgical Site Infection）が一旦発生すると，入院期間が延長し，医療費が増大するとともに，患者の手術治療に対する満足度を著しく損なうことになる．良質の医療を提供する面からも，また病院経営の面からもSSI発生率を低下させることが求められる時代となっている．

SSIサーベイランスとはSSIの発生を常時監視し､実態を把握することであるが,単なる調査ではなく，SSI発生率を低下させるという積極的な感染対策の意味合いを持つ活動である．

本報告ではSSIサーベイランスによって得られた日本と米国とのSSI発症率を比較して,その違いの有無を明らかとすることを目的とした。

B. 研究方法

日本のSSI発症率の現状については，全国71施設の集計結果であるJNISレポート（No.7）を参考とした．

JNIS(Japanese nosocomial infection surveillance)システムとはNNISシステムを基本として，日本の医療システム,疾病構造に合わせて構築されたサーベイランスシステムである.具体的には①NNISでは他の消化器手術（OGIT）に分類されている食道手術に対して，独自の分類（ESOP）を採用した，②大腸手術（COLO）を結腸手術（COLN）と直腸手術（REC）に細分類した，③感染原因に関する感染ルートの項目を調査項目に追加したなどの変更が加えられている．

米国のSSI発症率についてはNNISレポートを参考にした.定義，方法などは同様であるので,比較可能なデータである.また一方エビデンスレベルの高いとされる一流雑誌に掲載された論文でのSSI発生に関するデータについても比較する対象とした。

なお，SSI発生率を比較するためには,それぞれで扱った症例のSSI発生に関するリスクを調整して比較する必要がある.NNISシステムでは創分類,全身状態,手術時間を主たる因子とするリスクインデックス（表1）によるリスク調整を行なっており，このリスク調整に基づいて日米のSSI発生率を比較した．

C. 研究結果

JNISシステムによるSSIサーベイランスの集計結果（No.7）によると，1998年11月から2005年12

月までに登録された71施設52123例の集計では，SSIの発生例は4269例(8.2%)であった．経時的にみて、最近になりSSI発生率の増加が見られているのは，施設数の増加の中で消化器系手術の割合が増加しているためである（表2）

本邦の手術手技別SSI発生率を図1に示す．消化器外科手術はその他の手術と比較してSSI発生率が高いことが明らかであり，従来より指摘されているように、消化器外科手術におけるSSIを減少させることがSSI発生率を低下させる上で重要である．

各手術手技別にSSI発生部位を比較すると（図2），消化器系手術では，食道，胃，肝胆膵では臓器体腔SSIが多く，一方結腸，直腸，虫垂では切開創SSIが多い傾向が認められた．

本邦の手術手技（虫垂，胆嚢，胃，結腸，直腸）のNNISリスクインデックス別SSI発生率を図3に示す．症例数の少ない直腸手術のリスクインデックス3を除いて，リスクインデックスが高くなるに従って、SSI発生率が増加することが認められた．

手術手技虫垂，胃（図4）および胆嚢，大腸（図5）に関して，リスクインデックス別に米国のSSI発生率と本邦のSSI発生率を比較すると，すべての部分で本邦のSSI発生率が高値であり、中には4-5倍の差も認められる箇所があった。

一方、New England Journal of MedicineやJAMAなどに発表された論文でのSSI発生率をみると，結腸直腸手術において術中低体温の影響をみたKurzらの報告では，正常体温群6/104(6%)，軽度低体温群18/96(19%)，結腸直腸手術において周術期の80%酸素投与の効果をみたGreifらの報告では、30%酸素投与群 28/250(11.2%)，80%酸素投与群 13/250(5.2%)，Beldaらの報告では、30%酸素投与群35/143(24.4%)，80%酸素投与群 22/148(14.9%)であり，リスクインデックス0-1の症例であることを考慮すると，前述のNNISのデータよりもかなり高率の値であった。

D. 考察

本邦における多施設共同SSIサーベイランスは本邦における標準値を提示するとともに、米国NNISのSSI発生率と比較することも考慮して行われてきた。

JNISとNNISのデータを比較すると、本邦のSSI発生率はかなりの高値となるが、一方、エビデンスレベルの高い論文に報告された米国のSSI発生率をみると、NNISのデータよりもかなり高い値である。

実際には、本邦のSSI発生率は米国と比較して特に高いわけではなく、NNISのデータが，米国での入院期間が短く、また退院後のサーベイランスが十分ではないことなどからSSIの発生を十分には捕えられていないため、見かけ上低い値となっているためと考えられる。

その意味では、JNISのデータは、NNISのデータと比較して、30日までの経過観察が十分に行われている精度の高いデータといえる。

サーベイランスの持つ本質的な問題点として，精度の低い不十分なサーベイランスを行なうと，SSI発生率が見かけ上低くなることが挙げられる。SSIサーベイランスの目的はSSI発生率を低下させることなので，精度が低いための見かけ上の低いSSI発生率に満足することなく，質の高い精度の高いSSIサーベイランスを行なって，実態を正しく把握し，SSI減少のための努力を続けることが重要と考えられる。

E. 結論

本邦のSSIサーベイランスは米国のSSIサーベイランスと比較して、経過観察の十分に行われている精度の高いサーベイランスと考えられる。米国NNISのデータでは、SSI発生率が不十分な経過観察の

ために低く見積もられているので、日米の SSI 発生率を単純に比較することは困難であるが、本邦のSSI 発生率が米国と比較して特に高値であるとは思われない。

安全で質が高く，かつ適正なコストの外科治療を提供する上で，SSI 発生を少しでも少なくすることは重要な課題である．精度の高い SSI サーベイランスを継続的に行ない，SSI を減少させる努力を続けることが必要である．

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特記すべきことなし

G. 研究発表

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Nation-wide SSI surveillance in Japan and its financial effects

5th　EACIC　November 17-18　2006, Tokyo

表１　NNIS における SSI リスクインデックス異なる手術手技とは比較できない

- 手術創分類（手術創の汚染度，I-II→0,III-IV→1）
- 全身状態の評価（ASA 分類，PS1-2→0,PS3-6→1）
- 手術時間（平均手術時間の 75 パーセンタイル以下→0，平均手術時間の 75 パーセンタイルを超える→1）

創分類（0，1）＋ PS（0，1）＋時間（0，1）＝ 0，1，2，3

→　その患者の SSI のリスクインデックス

表２　SSI 発生率の推移（JNIS 集計データ）

	参加施設	総数	SSI 症例	SSI 発生率
～2001/3	9 施設	5,175 例	331 例	6.4%
～2002/3	27 施設	9,452 例	638 例	6.7%
～2003/3	33 施設	16,126 例	1,028 例	6.4%
～2003/12	36 施設	20,948 例	1,394 例	6.7%
～2004/12	50 施設	31,500 例	2,360 例	7.5%
～2005/12	71 施設	52,123 例	4,269 例	8.2%

表３　術中低体温と SSI

結腸直腸癌	Normothermia 36.6±0.5℃(n=104)	Hypothermia 34.7±0.6℃(n=96)	
SSI	6(6%)	18(19%)	(p=0.009)
hospitalization after surgery	12.1±4.4 日	14.7±6.5 日	(p=0.001)
Collagen deposition (μg/cm)	328±135	254±114	(p=0.04)
Suture removed	9.8±2.9 日	10.9±1.9 日	(p=0.02)

Kurz A, et al.　N Engl J Med 1996; 334: 1209-15

表４　周術期の８０％酸素投与と SSI（1）

術中および術後２ｈｒｓ 結腸直腸癌	30% oxygen (n=250)	80% oxygen (n=250)	
SSI	11.2%	5.2%	(p=0.01)
Length of hospitalization after surgery	11.9±4.0 日	12.2±6.1 日	
Collagen deposition	267±109	258±118	
Staples removed	10.4±1.5 日	10.3±1.4 日	

(Greif R, et al:　N Engl J Med 2000; 342:161-7)

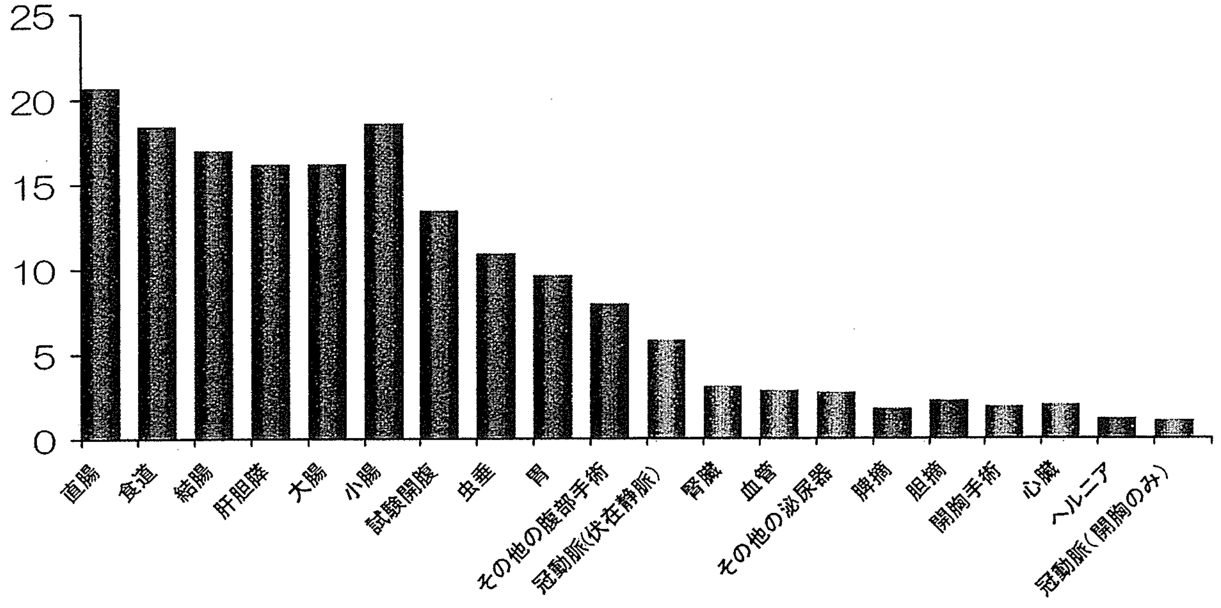

図1 手術手技別 SSI 発生率(1998/11 - 2005/12)

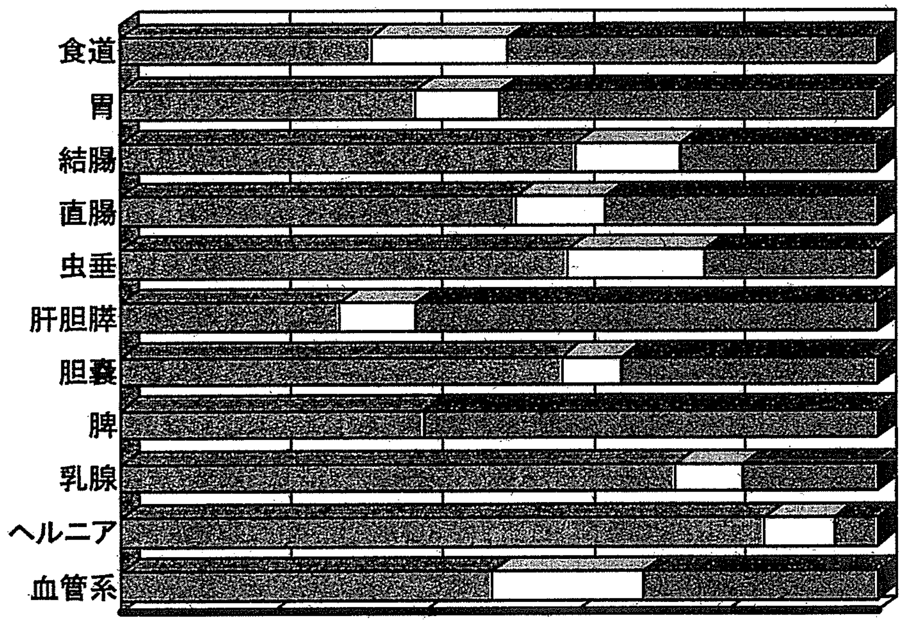

図2 手術手技別 SSI 感染部位の比率

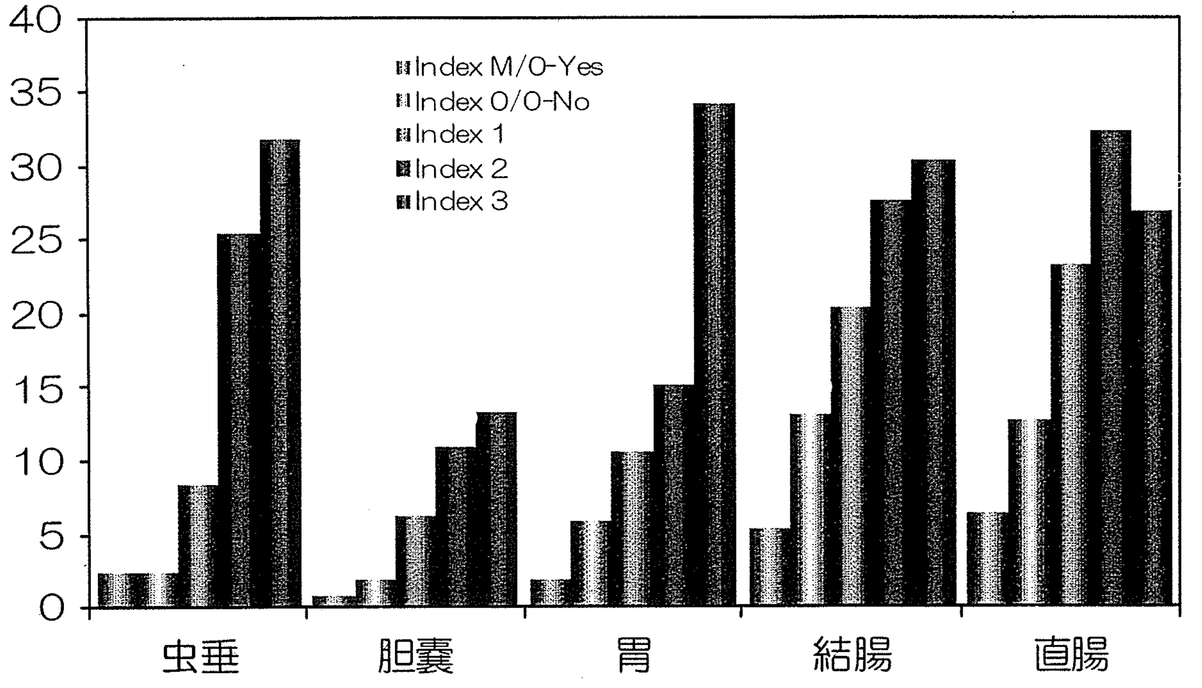

図3 NNIS リスクインデックス別 SSI 発生率

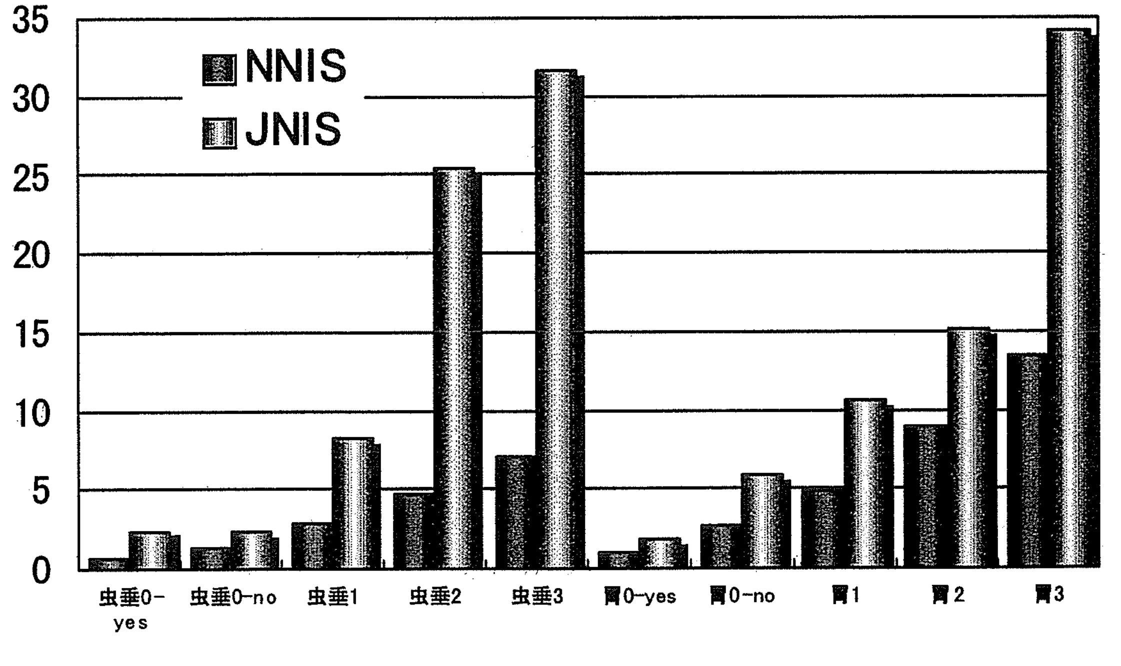

図4 NNIS と JNIS の SSI 発生率の比較(1)

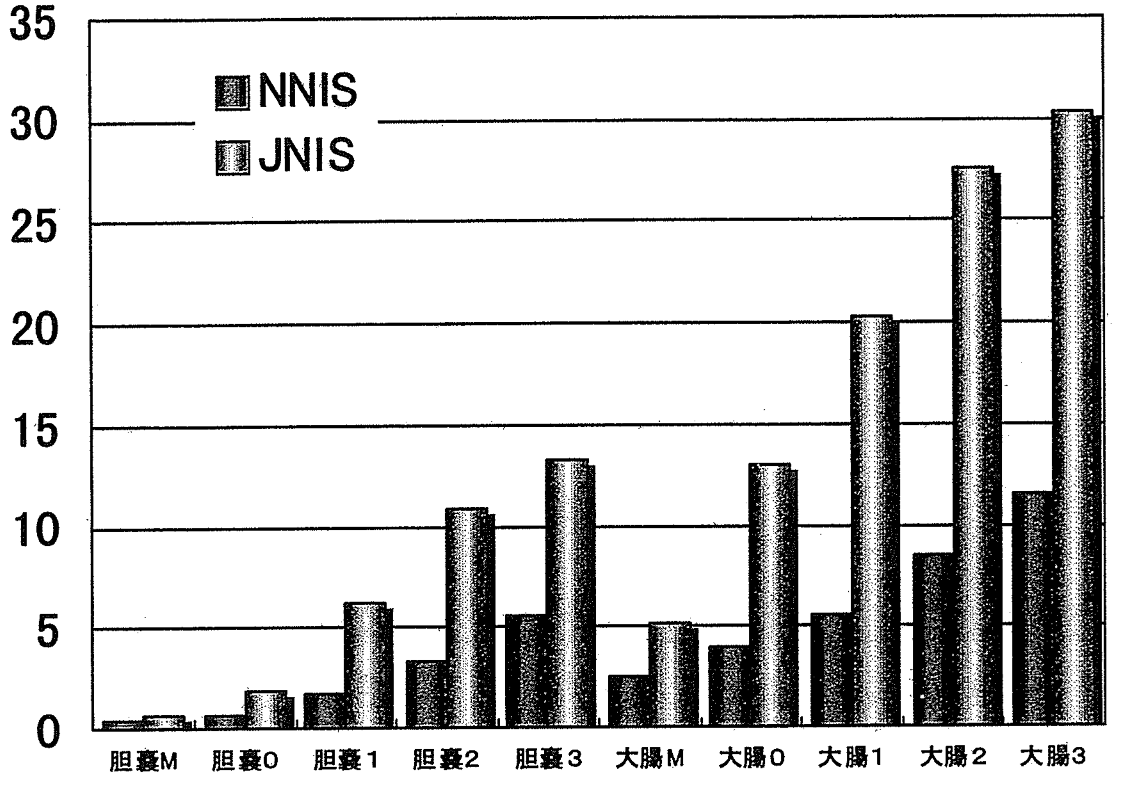

図5 NNISとJNISのSSI発生率の比較(2)

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Original Paper

Postoperative Host Responses in Elderly Patients after Gastrointestinal Surgery

M Ishikawa[1], M Nishioka[1], N Hanaki[1], T Miyauchi[1], Y Kashiwagi[1], H Miki[1]
Y Kawasaki[2], H Kagawa[2], H Ioki[2], Y Nakamura[2]
[1]Department of Surgery, and [2]Clinical Research Center, National Kochi Hospital, Japan
Corresponding Author: Masashi Ishikawa, MD, PhD, Department of Surgery, Tokushima Red Cross Hospital
1-28 Shinkai, Chuudenn, Komatsujima City, Tokushima, Japan
Tel: +81 8853 2 2555, Fax: +81 8853 2 6350, E-mail: masa1192@tokushima-med.jrc.or.jp

KEY WORDS:
Elderly patients; Th1/2 balance; Energy expenditure; Pulse dye-densitometry

ABBREVIATIONS:
Interferon (IFN); Interleukin (IL); Cardiac Index (CI); Cardiac Output (CO); Blood Volume (BV); Laparoscopic Cholecystectomy (LC); Systemic Inflammatory Response Syndrome (SIRS)

ABSTRACT

Background/Aims: The age-associated dysregulation of hemodynamic, metabolic and immune responses contributes to the high incidence of complications after major abdominal surgery.

Methodology: Ninety-five patients who underwent gastric resection (n=51) and colorectal resection (n=44) were divided according to age into Groups A (n=45, less than 70 years old), B (n=30, 70-79 years) and C (n=20, over 80 years). Flow cytometric analysis of CD4+ lymphocytes for interferon (IFN)-γ and interleukin (IL)-4 production determined the Th1/2 balance. Energy expenditure was measured by indirect calorimetry, and hemodynamics were studied using pulse dye densitometry.

Results: Surgical procedures, operating time, blood loss and morbidity did not significantly differ among the three groups. The cardiac index (CI) in group A and B increased significantly over preoperative levels until POD 3, but there were no significant perioperative changes in the CI levels of group C. Resting energy expenditure levels changed similarly to those of CI. The postoperative Th1/2 ratio decreased from young to elderly to very elderly patients, although no differences were significant before surgery. The postoperative percentage of CD4+IFN-γ+T cells (Th1) in group C decreased significantly despite of no significant changes in that of group A and B. In contrast, the ratio of CD4+IL-4+T cells (Th2) in the all groups significantly increased after surgery.

Conclusions: Host responses in elderly patients after major abdominal surgery were more hyperdynamic and hypermetabolic than those of young patients. Postoperative dysregulation of the Th1/2 balance was also associated with aging. However, host responses appear to significantly differ between elderly and very elderly patients.

INTRODUCTION

Chronological age is a predictor of a decreased postoperative survival rate. Aging causes disease, and the aging process adversely affects the survival of the organism and recovery from disease. Host responses to surgical stress and infection are altered with aging, and increased susceptibility to postoperative complications is age-related. Classical studies have demonstrated that aging results in decreased energy metabolism and hemodynamics such as cardiac output and circulating blood volume (1). Cardiac output trends downward with aging for various reasons. Early diastolic filling in individuals at age 70 is only one half of that of individuals at age 30. Diastolic dysfunction is the primary cause of heart failure in the elderly, but systolic function is normal or nearly normal in most of such patients. However, perioperative changes in cardiac output and circulating blood volume between young and elderly patients have rarely been compared. Hemodynamic changes can now be assessed at the bedside using dye densitometry as accurately as using the Swan Ganz method (2,3).

Surgical trauma induces metabolic alterations, including changes in energy metabolism. Several evaluations of energy changes have demonstrated that surgical procedures generally cause only a small increase (up to 30%) in resting energy expenditure, and efforts have been made to control for confounding factors that may influence energy metabolism (4,5). However, little is known about how perioperative energy metabolism changes in elderly patients.

Immunosenescence is associated with a deterioration of both cellular and humoral immunity (6,7). Although these changes are subtle, they ultimately result in altered responses to stress and infection. Mosmann *et al.* (8) classified murine CD4+ helper T cells as Th1 and Th2, according to cytokine profile. Other studies have shown that the secretion of Th1-cytokines such as interferon-γ (IFN-γ) and interleukin-2 (IL-2) is decreased in the elderly after lymphocyte stimulation (9,10). However, a few investigators have published controversial results regarding Th2-cytokines in the elderly (11,12). Further studies are required to clarify the interaction of the Th1/2 balance before and after surgery in the elderly. Many aspects of immune function, including the Th1/2 balance, would be dysregulated in the elderly, and cytokines are important in the development of pathological states. Therefore, we surmised that age-associated changes in the immune system will affect the host

Hepato-Gastroenterology 2006; 53:730-735

response after surgical procedures, including metabolic and hemodynamic changes. Here, we compared the perioperative immune, metabolic and hemodynamic responses of elderly and young patients who underwent abdominal surgery.

METHODOLOGY

Ninety-five patients (48 males, 47 females; mean age, 67±11 years) underwent abdominal surgery at our clinic between April 1999 and April 2002. The Research Committee of National Kochi Hospital approved the experimental protocol. All patients understood the nature and risk of this study, and written informed consent was obtained from all of them to participate. Fifty-one gastric resections for gastric cancer and 44 colorectal resections for colorectal cancer were performed. The patients were divided according to age into groups A (n=45), young patients (less than 70 years old), B (n=30), elderly patients (70-79 years old) and C (n=20), very elderly patients (over 80 years old). **Table 1** shows the characteristics of each group. The distribution of surgical procedures did not significantly differ among the groups. Six (13%) patients in group A, 7 (23%) in group B and 6 (30%) in group C had preoperative complications such as hypertension, angina, diabetes mellitus and cerebral infarction. Electrocardiograms and echograms did not reveal obvious changes in any of the patients. The procedures for groups A, B and C lasted 246±65, 178±166 and 251±283 min, respectively, with operative blood losses of 324±323, 278±331mL and 232±117mL, respectively. These data were not significantly different among the groups. None of the patients received steroids, low-dose dopamine or selective gut decontamination. Antibiotics were administered according to a predetermined protocol that was modified if specific microbiologic information became available. None received enteral nutrition and intravenous hyperalimentation during the study and patients who developed postoperative complications such as leakage, abdominal abscess and pneumonia, were excluded in the study. Thirty-seven patients [16 (36%) in group A, 13 (434%) in group B and 8 (40%) in group C] postoperatively developed systemic inflammatory response syndrome (SIRS) (13).

All patients were studied in the morning while resting in bed and before other examinations. Patients who were ventilated mechanically were excluded from the study.

Flow Cytometric Determination of Intracellular IFN-γ and IL-4 Expression

Blood was sampled before surgery, on POD 2 and 14. The proportion of CD4 positive lymphocytes producing IFN-γ and IL-4 were measured by flow cytometry as described by Openshaw *et al.* (14). Briefly, 1mL of blood was immediately mixed with 10μg/mL of Brefeldin A (Sigma B7651) at ambient temperature, within 2 hours of withdrawal. Peripheral blood lymphocytes were harvested, washed, and resuspended at a density of 10^5-10^6/mL and stimulated with PMA 50ng/mL (Sigma P8139) plus ionomycin (Sigma 10634) 500ng/mL. After a wash and a 10-min incubation in PBS containing BSA and saponin, lymphocytes were incubated with anti-CD4 monoclonal Ab and anti-IFN-γ DAKO, RG285) or anti-IL-4 (DAKO, RG204) for 30 min before adding an equal volume of 4% formaldehyde fixative. Samples were analyzed using a FACScan flow cytometer (Beckman Coulter). Results were analyzed using the XL/XL-MCL system and calculated as a ratio (%) of IFN-γ-producing (Th1) to IL-4-producing (Th2) cells.

Resting Energy Expenditure Measurements

We measured resting energy expenditure (REE) and the respiratory quotient (RQ) by indirect calorimetry using a ventilated hood system (Vmax29, SensorMedics, California, USA) preoperatively and on postoperative days 1, 3, 7, and 14. The REE value was calculated from the measured volume of oxygen utilization and carbon dioxide output, as described (15). Dry gases were measured and the results were converted to a standard temperature and pressure. Flow through the canopy was kept constant at a rate that was adjusted according to the body weight of the patient (28-36L/min). The predicted REE for each patient was calculated on the day of examination using the Harris-Benedict Equations (16).

Cardiovascular Studies

Cardiac output (CO), Cardiac index (CI), Blood volume (BV) and K-ICG were measured preoperatively and on POD 1 and 3 using a DDG-2001 apparatus (Nihon Koden, Tokyo, Japan) as described (17). Briefly, the probe was secured on one nostril or finger, and after sampling blood to measure hemoglobin, 20mg ICG was injected via an antecubital venous line while the DDG was recorded for 10 min. Pulse dye-densitometry is based on the principle of pulse spectrophotometry. The ratio of the blood ICG to the hemoglobin concentration was measured at wavelengths of 805 and 890nm. Because the extinction coefficient of ICG in blood is maximal at 805nm and almost zero at 890nm, and since the difference in the oxyhemoglobin and reduced hemoglobin extinction coefficients at these wavelengths is negligible, the ICG concentration can be calculated from the ratio of its concentration to the total hemoglobin concentration for each pulse. In addition, the elimination rate constant (K) of ICG (K-ICG), which is equivalent to

TABLE 1 Characteristics of Each Group

	Case	M:F	Disease	Operating Duration (min)	Blood loss (mL)
Young pts	45	23:23	gastric ca 27		
(less than 69yrs)			colon ca 18	246±65	324±323
Elderly pts	30	15:15	gastric ca 16		
(70-79yrs)			colon ca 14	178±166	279±332
Very elderly pts	20	11:9	gastric ca 8		
(over 80yrs)			colon ca 12	251±283	232±117

hepatic blood flow, was calculated from an ICG elimination curve detected by the DDG analyzer.

Statistical Analysis

Values for results are presented as means±SD. Continuous variables were compared using Student's *t* test. Differences between the two groups with respect to variable times were compared using the analysis of variance (ANOVA) for repeated measures. A *p* value of <0.05 was considered significant.

RESULTS

Changes in Hemodynamics

The cardiac index (CI) values of the young, elderly and very elderly patients were similar before surgery. The preoperative means±SD of CI were 2.81±0.60, 2.63±0.96 and 2.47±0.73L/min/m^2 for young, elderly and very elderly patients, respectively **(Figure 1)**. The CI in the young and elderly patient groups increased significantly over preoperative levels until POD 3. However, the perioperative CI levels did not significantly change in the very elderly patients. Significant differences in the preoperative values of BV were found among the three groups (A, 4.4±0.7; B, 3.7±0.9 and C, 2.9±0.8L; $P<0.05$). Postoperative BV values significant decreased in the order of young, elderly and very elderly patients (A, 4.0±0.9; B, 3.5±0.8 and C, 2.6±0.8L on POD 1; $P<0.05$). Postoperative BV values in each group did not significantly change. The preoperative K-1CG level of the young patients was significantly higher than those of the elderly and very elderly patients (A, 0.22±0.04; B, 0.18±0.05 and C, 0.17±0.04; $P<0.05$). The K-ICG levels in all groups significantly increased until POD 3 then they gradually decreased until POD 14.

FIGURE 1 Changes in cardiac index (CI) (■-■ young, ●-● elderly, ▲-▲; very elderly patients). CI in young and elderly patients significantly increased over preoperative levels until POD 3. However, perioperative CI levels did not significantly change in the very elderly patients.

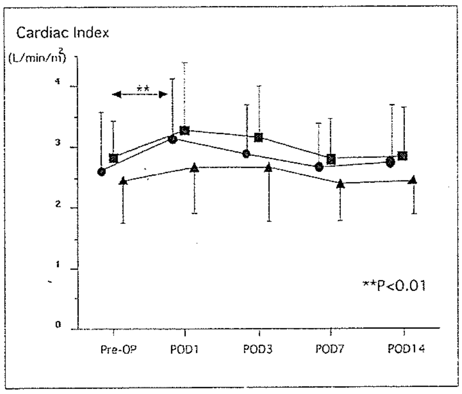


FIGURE 2 Changes in %REE (■-■ young, ●-● elderly, ▲-▲; very elderly patients). The REE levels in the elderly groups significantly increased until POD 3 compared with the preoperative level but postoperative levels in the other two groups did not significantly increase. On POD 1, the REE in the elderly groups was significant high compared with that in young and very elderly groups ($P<0.01$).

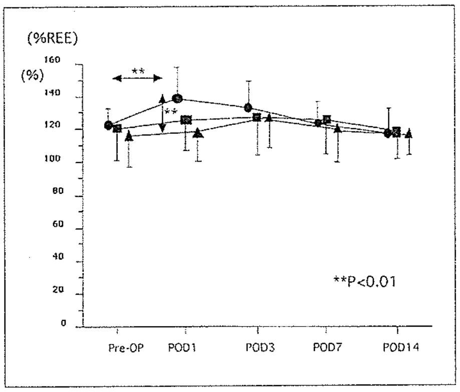
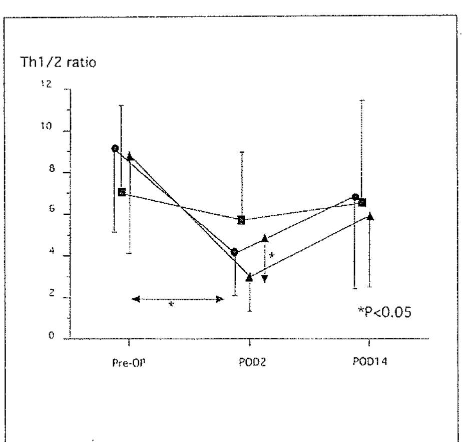


FIGURE 3 Changes in Th1/2 ratio according to age (■-■ young, ●-● elderly, ▲-▲; very elderly patients). Preoperative ratios of Th1 to Th2 among the three groups did not significantly differ, but the postoperative ratio of Th1 to Th2 decreased significantly in all patients from 8.2±4.to 4.5±3.0 on POD 2. The ratio of Th1 to Th2 in the super-elderly patients group obviously decreased to 3.0±1.7 on POD 2, which was significantly different ($p<0.05$) from those in young (5.7±4.2) and in elderly (4.1±2.0) patients. The Th1/2 ratio in all groups recovered to preoperative levels by POD 14.



Changes in Energy Metabolism Measured by Indirect Calorimetry

The mean amounts of weight lost by the patients by POD 7 was significantly ($p<0.05$) higher in group A [3.6±1.5 (6.6%)] and B [3.5±1.3 (6.8%)] compared with that of group C [2.6±1.5Kg (5.2%)]. Preoperative REE levels did not significantly differ among the three groups. The REE levels in the elderly groups significantly increased until POD 3 compared with the preoperative level but the postoperative levels of the other two groups did not significantly increase **(Figure 2)**. On POD 1, the REE in the elderly groups was significantly higher that that in the young and very elderly groups (A, 124±18%; B, 139±18%; C, 117±18%; $P<0.05$). The preoperative RQ level also did not significantly differ among the three groups. The RQ significantly decreased to around 0.8 immediately after surgery and returned to near preoperative levels on POD 14 in all groups.

Balance of Th1/2 Analyzed by Flow Cytometry

The lymphocyte counts in all groups were similar before surgery and decreased significantly after surgery, reaching a nadir of almost one-third of the baseline on POD 2. However, lymphocyte counts before and after surgery among the three groups did not significantly differ. The preoperative ratios of Th1 to Th2 among the three groups also did not significantly differ, the means being 7.1±5.1, 9.0±5.0 and 8.8±6.6 in the young, elderly and very elderly patients, respectively **(Figure 3)**. The postoperative ratio of Th1 to Th2 decreased significantly in all patients to 4.4±3.0 on POD 2 from 8.3±4.2. The ratio of Th1 to Th2 in the very elderly patients obviously decreased to 3.0±1.6 on POD 2, and was significantly different ($p<0.05$) from those in the young (5.7±4.1) and elderly (4.1±2.1) patients. The Th1/2 ratios in all groups recovered to preoperative levels by POD 14.

The ratios (%) of $CD4^+IFN\text{-}\gamma^+T$ cells among the three groups did not significantly differ before surgery (14.7±9.6%, 12.7±6.1% and 16.2±4.7% in young, elderly and super-elderly patients, respectively; **Figure 4a**). Although the percentage of CD4+IFN-γ +T cells did not significantly change in the young and elderly patients postoperatively, that of the very elderly decreased significantly to 10.4±6.3% on POD 2, and remained at a low level by POD 14. In contrast to CD4+IFNγ- +T cells, the ratio (%) of CD4+IL-4+T cells in all patients significantly increased to 4.8±3.5% on POD 2 from a preoperative value of 3.3±4.2% (**Figure 4b**).

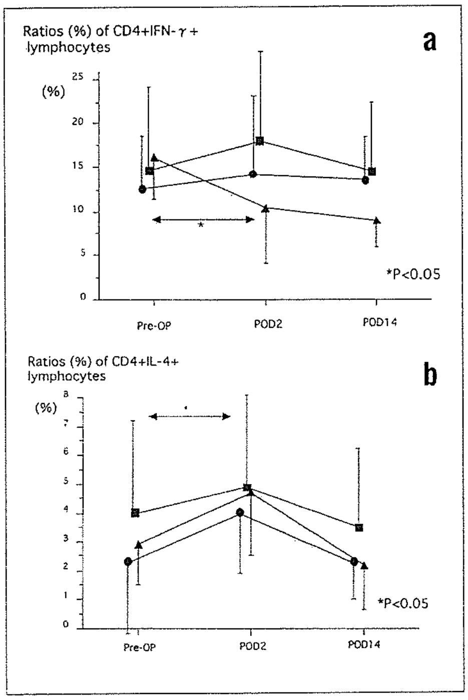


FIGURE 4 Preoperative and postoperative lymphocyte ratios (A, B and C, young, elderly and very elderly patients, respectively) **a)** and **b)**, Ratios (%) of CD4+IFN-γ + and CD4+IL-4+ lymphocytes, respectively. The postoperative ratio of CD4+IFN-γ +T cells (Th1) in group C significantly decreased whereas those in groups A and B did not. In contrast, the postoperative ratio of CD4+IL-4+T cells (Th2) significantly increased in all groups.

DISCUSSION

In elderly patients, the postoperative mortality rate increased with each decade beyond the age of 70 (18). Boyed *et al.* Showed a mortality rate of 5% in patients aged 70-79, and 17% in patients over 80 (19). Therefore, we selected patients older than 70 years and 80 years to evaluate the differences in host responses after gastrointestinal surgeries. Our data showed that the cardiac index and REE obviously increased at the early postoperative stage among elderly patients although the background did not significantly differ except for age between the young and very elderly patients. The cardiac index and REE did not significantly increase in the very elderly patients. Surgical stress causes an increase in cardiac output among both young and old patients but by very different mechanisms (20). Both the heart rate and stroke volume are increased in young patients by increasing the efficiency of contraction and by decreased end systolic volumes. However, the heart rate changes little in older patients; instead, stroke volume is increased. Although coronary artery disease increases considerably with advanced age, much of it does not become evident until after the stress of surgery.

Over the last 20 years, two major studies have focused on predicting cardiac risk for elderly patients undergoing noncardiac surgery. Goldman *et al.* (21) studied 1001 patients undergoing noncardiac surgery and established criteria that predict significant postoperative cardiac complications. Although age of over 70 years is a risk factor in the Goldman criteria, it does not carry statistical weight according to discriminant analysis as an active cardiac disease. Gerson *et al.* (22) showed that the most predictive test for postoperative cardiac and pulmonary complications among 100 patients above 65 years of age was exercise tolerance. Patients who could not exercise on a bicycle for 2 minutes and whose heart rate could not be increased beyond 100 beats per min were at a six-fold and five-fold increased risk for cardiac and pulmonary complications respectively. However, little is understood about perioperative hemodynamics among elderly patients undergoing major abdominal surgery. The integrated pulse spectrophotometry system used in the present study is less invasive and can be repeatedly applied within a short period without blood sampling (23). This method is useful for estimating the cardiac output, circulating blood volume and liver blood flow of gastrointestinal patients with a single bolus injection of ICG. No routine bedside monitoring has been used to estimate blood volume other than the Swan Ganz catheter. To our knowledge, the present study is one of the first perioperative comparisons of hemodynamics including cardiac index and blood volume between young and aged patients.

The amount of the early postoperative increase in REE was significantly in elderly patients compared with young and very elderly patients. Many studies have evaluated the energy expenditure associated with elective surgery (4,24). These studies have focused on not aging but surgical procedures. Surgical stress is characterized by hypermetabolism, accelerated tissue breakdown and loss of protein, resulting in weight loss and postoperative fatigue. Weight loss after abdominal surgery is usually due to a combination of increased energy expenditure secondary to the endocrine-metabolic response to injury, a decrease in dietary intake and increased metabolic requirements imposed by cancer. This study found that the mean weight loss of young and elderly patients during the period before surgery and POD 7 was significantly higher than that of very elderly patients. In general, the Harris and Benedict (HB) formula to predict REE in the elderly population may be questionable. Owen *et al.* (25) showed that REE is slightly underestimated by the HB formula in patients over 64 years of age. Fredrix *et al.* (4) showed that the HB formula underestimates REE by approximately 7% in healthy volunteers over 50 years of age. Therefore, the present study would have overestimated the %REE as a percentage of the reference value, and intragroup postoperative and preoperative %REE values were usually compared. Douglas and Shaw (26) found numerous factors to account for the increase in energy metabolism after surgical trauma. In addition to stress responses, energy metabolism is influenced by substrate metabolism, type and amount of calories, and other physiological differences such as increased body temperature. Most factors in the present study, such as calorie intake and the ratio of patients with fever did not significantly differ among the three groups. Therefore, we suspected that stress-induced mediators, such as IL-1, IL-6 and tumor necrosis factor, prostanoids, hormonal mediators, oxygen free radicals and their products caused the increase in energy metabolism. Indeed, Fagiolo *et al.* (27) reported significantly increased levels of IL-6, TNF-α and IL-1β in mitogen-stimulated cultures from aged donors. Although changes in postoperative RQ did not significantly differ according to age, the increase in REE was associated with a RQ in the 0.8 range, which was much higher than that of starvation (0.7) and much lower than that of glucose oxidation in the present study. This indicates that mixed fuel oxidation, namely with glucose, amino acids and fat did not significantly differ with age.

Although we did not measure circulating cytokine levels in our patients, we suspected that hemodynamics and energy expenditure were most prominent in the elderly patients due to age-related perturbation of mediators of the immune system. However, we also supposed that elderly individuals over 80 years old are less able to regulate hemodynamics and metabolism under stress although their systems function perfectly well at rest. The present study showed that the postoperative Th1/2 ratio decreased in the order of young to elderly to very elderly patients. Among the latter, the decrease in the number of $CD4^+IFN\text{-}\gamma^+$T cells was accompanied by a simultaneous postoperative increase in that of $CD4^+IL\text{-}4^+$T cells although the number of $CD4^+IFN\text{-}\gamma^+$T cells in the young and elderly patients did not significantly change. The results of the present study are consistent with those of previous reports demonstrating that major surgery suppresses the potential responses of Th1 cytokines and significantly decreases IFN-γ and IL-2 production by mononuclear cell cultures from elderly individuals (28,29). In general, the delayed type hypersensitivity response, lymphocyte proliferation and cytotoxic T lymphocyte activities decrease with aging while the numbers of memory T cells and the antibody response increases (30). However, reports of age-related changes in the production of proinflammatory cytokines are inconsistent. Caruso *et al.* (11) showed that IFN-γ and IL-2 production of mononuclear cells from elderly individuals significantly decreased but IL-4 and IL-6 production did not significantly differ between cultures from elderly and from young patients. Cakman *et al.* (9) also showed decreased production of IFN-γ and soluble IL-2 receptor in the elderly, whereas that of IL-10 was greater than in young controls. These findings suggest that a dysregulated Th1/2 balance causes the type of immune response observed in the elderly individuals. However, perioperative changes in the Th1/2 balance of elderly patients have not been studied. We recently demonstrated that the preoperative Th1/2 ratio of patients with a malignancy was significantly lower that that of patients with laparoscopic cholecystectomy (LC), and that the Th1/2 ratios on POD 2 of patients who underwent gastric and colorectal resection were significantly decreased compared with those who underwent LC (31). Decker *et al.* (32) also reported that the Th1/2 balance was quite different between LC and open cholecystectomy patients, showing that down-regulation of the Th1 immune response or cell-mediated immunity increases patient susceptibility to infection by viruses or intracellular bacteria. The age-related changes in the Th1/2 balance may be directly or indirectly associated with impaired protective immunity, by affecting the ability to deal with infections or tumors. The reduced amounts of IFN-γ on $CD4^+$T cells shown in the present study, might significantly contribute to the increased susceptibility of elderly individuals to infections and tumors.

In conclusion, the host responses of elderly patients after major abdominal surgery were more hyperdynamic and hypermetabolic than those in young patients. In contrast, the postoperative host responses of very elderly patients were mild. Cytokines, including the Th1/2 balance became dysregulated with aging. These findings suggest that host responses significantly differ between elderly and very elderly patients. Therefore, the postoperative management of aged patients should consider the metabolic, hemodynamic and immunological changes associated with aging.

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Original Paper

Results of 404 Hepatic Resections Including 80 Repeat Hepatectomies for Hepatocellular Carcinoma

Akira Kobayashi MD[1], Seiji Kawasaki MD[2], Shin-ichi Miyagawa MD[1], Shiro Miwa MD[1]
Terumasa Noike MD[1], Satoshi Takagi MD[1], Satoru Iijima MD[1], Yusuke Miyagawa MD[1]
[1]First Department of Surgery, Shinshu University School of Medicine, Matsumoto
and [2]Second Department of Surgery, Juntendo University School of Medicine, Tokyo, Japan
Corresponding Author: Seiji Kawasaki MD, Second Department of Surgery
Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, Japan
Tel: +81 3 5802 0434, Fax: +81 3 5802 0434, E-mail: kawasaki@med.juntendo.ac.jp

KEY WORDS:
Liver resection; Hepatocellular carcinoma; Repeat hepatectomy

ABBREVIATIONS:
Hepatocellular Carcinoma (HCC); Indocyanine Green Retention Rate at 15 minutes (ICG-R); Blood Transfusion (BTF); Ultrasonography (US); α-Fetoprotein (AFP); des-gamma-Carboxy Prothrombin (DCP); Computed Tomography (CT); Hepatitis B Antigen (HBsAg); Hepatitis C Antibody (HCVAb)

ABSTRACT

Background/Aims: To evaluate our treatment protocol applied to patients with hepatocellular carcinoma. The protocol consists of the selection criteria for hepatectomy, the use of techniques that minimize intraoperative blood loss, strict follow-up after surgery, and an aggressive surgical approach for intrahepatic recurrence.

Methodology: We conducted a retrospective cohort study that included 337 patients with hepatocellular carcinoma treated between 1990 and 2001. The type of resection was selected according to the serum bilirubin value and the indocyanine green retention rate at 15 minutes. Perioperative data and long-term outcome were examined.

Results: We performed 324 initial hepatectomies with an in-hospital mortality rate close to zero. There was one operative death and one hospital death (0.3% each), and the 5-year survival rate for all patients was 53.2%. Eighty repeat liver resections, including 18 third and two fourth, were performed with no mortality, and the 5-year survival rate was 52.9% after the second hepatic resection. The resectability rate for second and third hepatectomies reached 29% and 33% of all patients with isolated liver recurrence, respectively.

Conclusions: Liver resection is a safe and effective treatment modality for hepatocellular carcinoma. Our results are likely attributable to the routine application of our treatment protocol.

INTRODUCTION

With advances in surgical techniques and perioperative care, there has recently been a great improvement in the results of liver resection. For hepatocellular carcinoma (HCC), one of the most common malignancies worldwide, perioperative mortality rates of around 5% are frequently reported (1-3), and many liver surgeons seem to consider these rates acceptable. However, recent studies from specialized medical centers have reported zero mortality rates (4,5). It is therefore important that we re-evaluate the safety of liver resection in patients with HCC.

Hepatic resection has long been held to be the only potentially curative option for HCC. The long-term outcome of 'curative' resection is, however, far from satisfactory because of the high incidence of intrahepatic recurrence (6,7). To improve the surgical outcome of HCC patients, we need to establish effective treatment strategies for such recurrences.

During the last 11 years we have routinely applied our own treatment protocol to HCC patients, which consists of a set of selection criteria for hepatectomy (8,9), combined with surgical techniques aimed at minimizing intraoperative blood loss (9-11), careful follow-up, and an aggressive surgical approach for recurrence (12,13). Using this protocol, we have performed 324 initial and 80 repeat hepatectomies, including 18 third and two fourth resections. Here, we review our 11-year experience of liver resection for HCC and clarify the safety and potential benefits of hepatectomy.

METHODOLOGY

Between January 1990 and December 2001, we have performed 404 potentially curative hepatectomies: 324 initial and 80 repeat liver resections, on 337 HCC patients at the First Department of Surgery, Shinshu University. Potentially curative resection means removal of all gross tumors. These 337 patients, including 13 patients who underwent their initial (8 patients) or second hepatectomy (5 patients) at other institutions, are the subjects of this report. There were 258 men and 79 women, and their mean age was 64 years (range, 21- 85 years). The type of liver resection was defined according to the scheme shown in **Figure 1** (8). If ascites could not be controlled with diuretics preoperatively, liver resection was not indicated. The serum bilirubin value and the indocyanine green retention rate at 15 minutes (ICG-R) were the major parameters for determining the extent of resection. The details of the surgical tech-

Hepato-Gastroenterology 2006; 53:736-741

Original Paper

Perioperative Hemodynamic Study of Patients Undergoing Abdominal Surgery using Pulse Dye Densitometry

Masanori Nishioka MD[1], Masashi Ishikawa MD, PhD[2], Norikazu Hanaki MD[1] Yutaka Kashiwagi MD, PhD[2], Hisashi Miki MD, PhD[2], Hidenori Miyake MD, PhD[1] Seiki Tashiro MD, PhD[1]

[1]Department of Digestive Surgery, University of Tokushima, School of Medicine and [2]Department of Surgery, National Kochi Hospital, Japan

Corresponding Author: Masanori Nishioka, MD, Department of Digestive Surgery, University of Tokushima School of Medicine, 1-50-2 Kuramoto cho, Tokushima City, 770-8503 Japan

Tel: +81 88 631 3111, Fax: +81 88 631 9698, E-mail: khotchi@clin.med.tokushima-u.ac.jp

KEY WORDS: Pulse dye densitometry; Hemodynamic change; Digestive surgery

ABBREVIATIONS: Pulse Dye Densitometry (PDD); Indocyanine-Green (ICG); Cardiac Output (CO); Cardiac Index (CI); Blood Volume (BV); ICG elimination rate (K-ICG); Postoperative Day (POD); Systemic Inflammatory Response Syndrome (SIRS)

ABSTRACT

Background/Aims: Pulse dye densitometry (PDD) using indocyanine-green (ICG) is a newly developed technique for monitoring cardiac output (CO), cardiac index (CI), circulating blood volume (BV) and ICG elimination rate (K-ICG). We measured hemodynamic changes during the perioperative period in patients undergoing digestive surgery to analyze relationships between hemodynamic changes and surgical procedures, blood loss, water balance and SIRS.

Methodology: Eighty-seven patients who underwent gastrectomy (n=46) and colectomy (n=41) without postoperative complications were enrolled in this study. The corresponding data from 15 patients who underwent laparoscopic cholecystectomy were used as controls. CO, CI, BV and K-ICG were measured by PDD before operation, on the first postoperative day (POD 1), POD 3, POD 7 and POD 14.

Results: In all patients, CO and CI increased significantly until POD 3 compared with preoperative levels. BV on POD 1 decreased significantly compared to the preoperative level. K-ICG increased significantly until POD 14. Laparoscopic cholecystectomy resulted in less surgical stress than gastrectomy or colectomy as measured by hemodynamic changes. There were minimal differences in hemodynamics between the gastrectomy and colectomy groups. There were significant negative correlations between intraoperative blood loss and the [POD 1: preoperative values] ratios for CO, CI, BV or K-ICG. There was no correlation between changes in water balance from operation to POD 1 and [POD 1: preoperative value] BV ratio.

Conclusions: An increase in CO and decrease in BV were observed at the early operative stage, especially in patients with systemic inflammatory response syndrome (SIRS). Interestingly, hepatic artery flow volume (K-ICG) remained high until POD 14. It is important to minimize intraoperative blood loss, since it markedly affects postoperative hemodynamics.

INTRODUCTION

The importance of monitoring hemodynamic changes in critically ill patients during perioperative management is widely recognized and many methods have been developed to monitor these changes. Conventionally, the Swan-Ganz method has been used to evaluate hemodynamic changes in ICU patients. However, it is invasive and is complicated to perform at the bedside (1-3). Pulse dye densitometry (PDD), a method newly developed by Aoyagi *et al.*, provides a noninvasive means for repeated measurements of cardiac output, cardiac index, circulating bloody volume by determining the indocyanine green elimination rate (K-ICG) following injection ICG into a peripheral vein (4,5). The accuracy and reproducibility of this method in estimating cardiac output and blood volume in comparison to the Swan-Ganz method and radioisotope method has been confirmed by other reports (6-15). Measurements of circulating blood volume may be of particular value in circumstances in which acute hemodynamic changes can potentially occur, for example in sepsis and major surgery. After cardiac surgery during which there was extracorporeal circulation with hemodilution, it is well understood that BV decreases while water accumulates in the interstitial space (16). However, repeated measurements of cardiac output and blood volume at the bedside of critically ill patients is unfeasible, therefore, potential hemodynamic changes in such patients have only been the subject of speculation. Information on hemodynamic change would be beneficial for management of patients experiencing cardiac or other complications. Until now, reports on perioperative hemodynamic change following digestive surgery have been very limited.

The first purpose of the present study is to investigate the perioperative hemodynamic changes by PDD using ICG in relation to type of surgical procedures in patients undergoing digestive surgery. Prolonged

Hepato-Gastroenterology 2006; 53:874-878

hypoperfusion of the gut and liver during operation are reported to lead to severe complications and an increased mortality rate in resuscitation from hemorrhagic shock (17). Although correction of volume depletion is the main method of resuscitation, the methods used vary widely and are dependent on clinician's experience. The second purpose of this study is to analyze relationships between hemodynamic change and operative factors such as blood loss and perioperative water balance.

Systemic inflammatory response syndrome (SIRS) describes a clinical response arising from non-specific insult, but it also includes a number of pathologic states because of its loose definition. Although patients with major surgeries show high rates of postoperative SIRS, it is transient, followed by complete recovery, in 1 to 3 days. However, little is known about differences in hemodynamic changes between postoperative SIRS and non-SIRS patients. Hence, the third purpose of this study is to evaluate differences in hemodynamic changes in such patients during the early postoperative stage.

METHODOLOGY

Patient Population and Data Collection

From May 1999 through March 2001, 87 patients who underwent gastrectomy for gastric cancer [n=46, 31 men and 15 women aged 64±13 years (mean ±SD)], colectomy for colorectal cancer (n=41, 20 men and 21 women aged 68±16 years) at the Department of Surgery, National Kochi Hospital were enrolled in this prospective study. The control group consisted of 15 patients who underwent laparoscopic cholecystectomy for cholecystolithiasis (7 men and 8 women aged 53±16 years). All experimental protocols were approved by the Research Committee of National Kochi Hospital. Exclusion criteria were as follows: serious hepatic dysfunction, coexisting severe cardiovascular and pulmonary disease, requirement for mechanical ventilation, and postoperative complications. The heights of the subjects ranged from 135 to 177cm (mean 158±10cm) and their body weights varied from 22 to 84kg (55±12kg). Cardiac output (CO), cardiac index (CI), circulating blood volume (BV) and K-ICG were measured five times; preoperatively, and on postoperative days (POD) 1, 3, 7, and 14. Measurements were performed by pulse dye densitometry with indocyanine-green (DDG-2001, Nihon Kohden Corp., Tokyo, Japan). All patients were studied while resting in bed, and measurements were taken in the morning before other examinations. Measurements of CO, CI and BV were calculated as described previously. Briefly, a probe was secured on one nostril or finger, and after sampling blood to measure hemoglobin, 20mg ICG was injected via an antecubital venous line while DDG was recorded for 10 min.

Pulse dye densitometry is based on the principle of pulse spectrophotometry. Wavelengths of 805 and 890nm were used to measure the ratio of blood ICG concentration to hemoglobin concentration. Because the extinction coefficient of ICG in blood is at its maximum at 805nm and is almost zero at 890nm, and the difference in oxyhemoglobin and reduced hemoglobin extinction coefficients at these wavelengths is negligibly small, ICG concentration can be calculated from the ratio of its concentration to total hemoglobin concentration for each pulse. In addition, the elimination rate constant (K) of ICG (K-ICG), which is equivalent to hepatic blood flow, is calculated by ICG elimination curve as detected with a DDG analyzer (6-13).

As defined by ACCP/SCCM consensus conference in 1992, SIRS was diagnosed if 2 or more of the criteria were met (18). Forty-three patients (23 gastric resections and 18 colorectal resections) exhibited SIRS on POD 1, whereas 44 patients showed no sign of postoperative SIRS on POD 1. On POD 3, there were 19 patients with SIRS and 68 patients without SIRS. No patients in the laparoscopic cholecystectomy group developed SIRS.

Surgical Management

All patients received the general anesthetic sevoflurane by endotracheal inhalation while the gastrectomy and cholecystectomy groups additionally received epidural anesthesia. Laparoscopic cholecystectomy was performed by the abdominal wall lifting method, gastrectomy with D1 or D2 lymph node dissection as described in the second English edition of the *Japanese Classification of gastric carcinoma* and colectomy with D2 or D3 lymph node dissection as described in the *Japanese Classification of colorectal carcinoma*. Epidural analgesia was provided before surgery and maintained for 72 hours postoperatively as analgesia. Perioperatively, continuous intravenous fluid resuscitation was given to maintain urine output (>1.0mL/kg per hr). We performed blood transfusion and infusion of hydroxyethylstarch solution based on the volume of blood loss during and/or after surgery. The mean estimated operative blood loss was 261±265mL for the gastrectomy group, 301±375mL for the colectomy group and 73±134mL for the laparoscopic cholecystectomy group (range; 0-1580mL). Two patients (gastrectomy and colectomy) received blood transfusions intraoperatively. The mean estimated operation time was 229±51 min for the gastrectomy group, 228±91 min for the colectomy group and 128±54 min for the laparoscopic cholecystectomy group (range; 65-630 min). Patients received intravenous fluid in amounts ranging from 450 to 4620mL (mean 1604±848mL). The intraoperative mean total water balance, namely the average amount of drip infusion and urine production including blood balance, was 1118±639mL (range; 115-2795mL). None of the patients received steroids, low-dose dopamine or selective gut decontamination. Antibiotics were administered according to a predetermined protocol that was modified if specific microbiologic information became available. No patient received enteral nutrition during the study.

Statistical Analysis

Unless otherwise noted, data values are presented as mean ± SD. The statistical significance of difference between data was assessed with Student's paired t test. Linear regression analysis was used to determine the relationships between intraoperative blood loss and hemodynamic changes, and between water balance and BV. Calculations were performed using the statistical software package Stat View (Abacus Concepts, Berkeley, CA). A p value of less than 0.05 was considered significant.

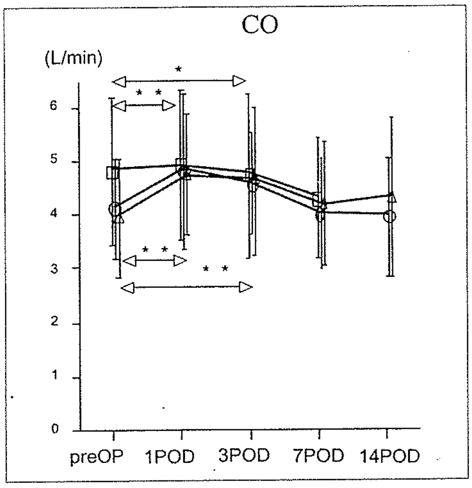

FIGURE 1
Changes in cardiac output (CO) and cardiac index (CI) in surgical patients. There were significant increases in CO and CI until POD 3 compared with preoperative levels.

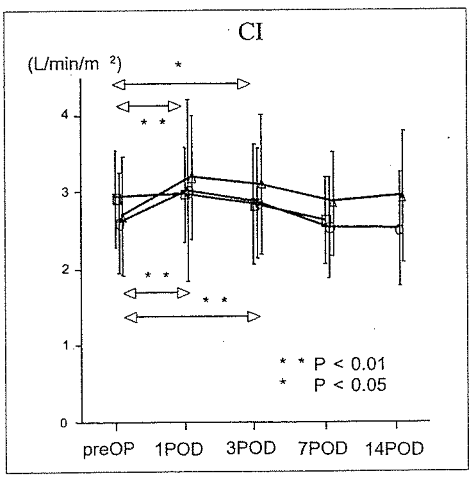

FIGURE 2
Changes in cardiac output (CO) (●; gastrectomy, □; colectomy, ○; Laparoscopic cholecystectomy). An increase of CO in gastrectomy and colectomy groups was seen until POD 3 despite no significant changes in the laparoscopic cholecystectomy group.

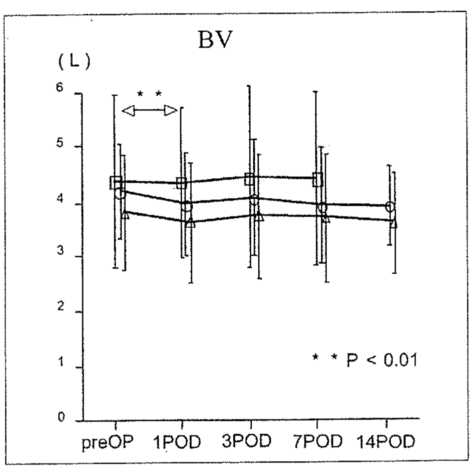

FIGURE 3
Changes in circulating blood volume (BV) (●; gastrectomy, □; colectomy, ○; Laparoscopic cholecystectomy). A decrease of BV in gastrectomy group was seen until POD 1 despite no significant changes in the colectomy and laparoscopic cholecystectomy groups.

RESULTS

In the gastrectomy and colectomy groups, the mean CO and CI values increased significantly until POD 3 compared with their preoperative values (CO: 4.8±1.3 on POD 1 and 4.6±1.2 on POD 3 *vs.* 4.0±1.0 L/min before operation, CI: 3.1±1.0 on POD 1 and 3.0±0.8 on POD 3 *vs.* 2.6±0.7 L/m^2 before operation) **(Figure 1)**. The values at any time point were not significantly different between the gastrectomy and colectomy group. No significant postoperative changes were observed in CO and CI in the laparoscopic cholecystectomy group **(Figure 2)**. The mean preoperative BV value for the gastrectomy group was 74±17mL/kg, which significantly decreased to 69±18mL/kg on POD 1 and immediately recovered to 71±18mL/kg on POD 3 **(Figure 3)**. No significant decreases in BV were observed in the colectomy or laparoscopic cholecystectomy groups. The K-ICG value increased significantly until POD 3 for the laparoscopic cholecystectomy group, until POD 7 for the gastrectomy group and until POD 14 for the colectomy group **(Figure 4)**. There were significant negative correlations between intraoperative blood loss and the [POD 1/preoperative value] ratios for CO, CI, BV or K-ICG. There was a correlation between the [POD 1/preoperative value] CO ratio and intraoperative blood loss (R=0.38, p=0.001) **(Figure 5)**. All subjects who developed intraoperative blood loss of over 700mL showed a decrease in CO on POD 1 as compared with their preoperative value. The correlation coefficients of the [POD 1/preoperative value] CI ratio and BV ratio to intraoperative blood loss were 0.38 (p=0.001) and 0.42 (p<0.0001), respectively. All patients who developed blood loss of over 700mL showed a decrease in BV as well as changes in CO. A moderate correlation was also seen between intraoperative blood loss and the [POD 1/preoperative value] K-ICG ratio (R=0.29, p=0.01). There was no correlation between changes in water balance from operation to POD 1 and the ratio [POD 1/preoperative value] for CO, CI, BV and K-ICG.

Although CI on POD 3 in patients with postoperative SIRS was significantly higher than in patients without postoperative SIRS (3.4±0.9 *vs.* 2.84±0.8, p<0.01), no significant differences in BV and K-ICG levels were seen between the two groups.

DISCUSSION

The normal physiological response to stress and injury results in a series of cardiovascular changes including increases in heart rate, heart contractility and cardiac output. However, little is known about alterations in BV and hepatic blood flow volume. The present study shows that in patients who undergo gastrectomy or colectomy, CO, CI and K-ICG increase in the early postoperative stage despite a decrease in BV. This indicates a hyperdynamic postoperative state. However, CO, CI and BV return to their preoperative levels soon after surgery (POD 1 for BV and POD 3 for CO and CI). Judging from these findings, cardiac output transiently increases immediately after gastrectomy and colectomy while hepatic artery flow volume