

## Video-assisted thoracic surgery attenuates perioperative oxidative stress response in lung cancer patients: a preliminary study

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**Objectives:** Reactive oxygen species (ROS) function as key metabolites that can impair biological processes. The aim of this preliminary study was to assess the perioperative oxidative changes in lung cancer surgery.

**Methods:** We measured the levels of blood hydroperoxides, a type of ROS, as an index of oxidative injury to cellular components, as well as the plasma ferric-reducing ability as an index of total antioxidant potential in 32 lung cancer patients. Hydroperoxides were measured by the levels of diacron reactive oxygen metabolites (d-ROMs). The antioxidant potential was determined by the biological antioxidant potential (BAP), which represents the levels of endogenous antioxidant enzymes.

**Results:** Lung cancer patients had slightly affected oxidative stress before surgery. The d-ROM and BAP levels after surgery and were significantly decreased than before surgery ( $p < 0.001$ ) and the levels recovered preoperatively at third post-operative day. The d-ROM level in video-assisted surgery group ( $n=17$ ) was significantly decreased than those in thoracotomy group ( $n=15$ ) at third and seventh post-operative day ( $p < 0.001$ , and  $< 0.02$ ).

**Conclusions:** Lung cancer patients had already exposed oxidative stress before surgery and surgical intervention also generates large amounts of ROS. Video-assisted thoracic surgery can reduce the ROS compared to the standard thoractomy.

ACTA MEDICA NAGASAKIENSIA 59: 19–25, 2014

**Key words:** lung cancer, oxidative stress, video-assisted thoracic surgery

### Introduction

Oxidative stress can be defined as an imbalance between the pro-oxidant and the antioxidant potential of cells, which results either from an overproduction of reactive oxygen species (ROS), insufficient detoxification of ROS by antioxidants, or a combination of both [1]. It is widely known that ROS function as key metabolites that can impair biological processes, resulting in various diseases, including cardiovascular disease, diabetes, neurological disorders, and cancer [2, 3]. Various types of markers have been used to

evaluate oxidative stress, such as lipid peroxides, 4-hydroxynonenal, malondialdehyde, isoprostanes, 8-hydroxyguanine, thymine glycol, carbonyl protein, dopa, hydroxy-leucine, and hydroxyvaline [2]. However, to date, it has been difficult to directly measure levels of ROS due to their short half-life.

Currently, blood levels of hydroperoxides, a type of ROS, can be easily and accurately measured in patients as an index of oxidative injury to cellular components. In addition, plasma ferric-reducing ability can be assessed as an index of total antioxidant potential. Both hydroperoxides and ferric-re-

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Received March 24, 2014; Accepted April 15, 2014

ducing capacity can be measured with a small volume of patient's blood using a Free Radical Elective Evaluator (FREE® Carpe Diem; Wismerll Co. Ltd., Tokyo, Japan).

Clinical reports have shown an association between oxidative stress and various diseases [1, 2, 4-10]. For example, it is noteworthy for surgeons that an increase in preoperative ROS was associated with nodal extension in patients with clinical stage I lung adenocarcinoma [4]. Moreover, Misthos et al. [11] reported that protracted single-lung ventilation should be considered a potential cause of cardiovascular complications through the generation of severe oxidative stress due to lung re-expansion. Therefore, the measurement of oxidative stress has the potential to identify tumor characteristics and to predict perioperative complications.

However, there have been few reports on perioperative oxidative stress, especially in lung cancer patients. Moreover, minimally invasive surgical procedures have been adopted worldwide, especially video-assisted thoracic surgery (VATS), and these less invasive procedures might be associated with less oxidative stress.

The purpose of the present study was to evaluate perioperative oxidative stress and to determine whether VATS reduces oxidative stress compared with standard thoracotomy in lung cancer patients.

## Patients and methods

### *Patients*

The study was performed at Nagasaki University Hospital from January 2011 to December 2012. Local ethics committee approval was obtained prior to beginning of the study (Approval number: 10112951). All patients gave written informed consent. For participation in this study, age, gender, comorbidity, clinical stage, extension of lung resection and type of thoracotomy were not considered. Exclusion criteria were the surgery for benign thoracic neoplasm and the refusal of patients. A total of 32 patients (20 men, 12 women; mean age, 69.1 years) participated in the study. All patients had primary non-small cell lung cancer (NSCLC) and underwent elective lung cancer surgery.

### *Surgical technique for lung cancer*

General anesthesia was induced using propofol and rocuronium. All VATS procedures were performed by visualization through a television monitor only, and the procedures were performed without metal retractors using the wound retraction system (WR) (Alexis Wound Retractor®; Applied

Medical, Rancho Santa Margarita, CA, USA), with an incision length of  $\leq 4$  cm. Standardized three-port placements (Thoracoport®, 11.5 mm; Nippon Covidien, Tokyo, Japan) were used regardless of the resected lobe and segment. In contrast, once metal retractors were applied, or even if metal retractors were not used but a skin incision  $>7$  cm was made, the procedure was defined as thoracotomy. Systemic mediastinal or hilar lymph node dissection was performed according to the clinical stage, performance status, and lymph node status of the patient. The indication for VATS was clinical stage I cancer. The details of our procedures for lung cancer were reported previously [12].

### *Measurement of oxidative stress and plasma antioxidant activity*

We measured that the levels of blood hydroperoxides, a type of ROS, as an index of oxidative injury to cellular components in lung cancer patients who underwent pulmonary resection. Hydroperoxides were measured by the plasma levels of diacron reactive oxygen metabolites (d-ROMs). This test was performed using a Free Radical Elective Evaluator (FREE® Carpe Diem; Wismerll). Details of the entire procedure have been described previously [2, 10]. In brief, d-ROM levels are detected based on the ability of transition metals to catalyze, in the presence of peroxides, the formation of free radicals that are then trapped by an alchilamine. The alchilamine reacts to form a colored radical that can be detected by a spectrophotometer at 505 nm. The results are expressed in arbitrary units, namely Carratelli units (U. CARR) [10]. A single U.CARR corresponds to 0.08 ng/100 mL of  $H_2O_2$  [13].

We also measured the biological antioxidant activity of plasma (BAP) using the Free Radical Elective Evaluator [2,10]. In brief, when trivalent  $FeCl_3$  is dissolved in a colorless solution containing a chelation acid derivative, it turns red as a result of the action of the  $Fe^{+3}$  ions. However, it is decolorized by the reduction of  $Fe^{+3}$  to  $Fe^{+2}$  ions caused by the antioxidant activity of plasma added to the reaction solution. The antioxidant potential of plasma is evaluated by measuring the degree of decolorization using a spectrophotometer. The normal value for BAP in healthy subjects is  $>2200 \mu\text{mol/L}$  (Table 1).

Blood samples were obtained from each patient at five time points: preoperatively, right after surgery, on the first postoperative day (POD), on the third POD and on the seventh POD. This measurement point was determined by the routine blood collection point after lung cancer surgery in our department except for the time of right after surgery.

**Table 1.** Defined levels of d-ROM and BAP

d-ROM	Value	BAP	Value
Normal range	200-300	Border-line	2200-2000
Border-line stress	301-320	Slight reduction	2000-1800
Low stress	321-340	Moderate reduction	1800-1600
Middle stress	341-400	Strong reduction	1600-1400
High stress	401-500	Very strong reduction	>1400
Very high	>501		

d-ROM: diacron reactive oxygen metabolite

BAP: biological antioxidant potential

Blood samples were centrifuged and serum was stored at -80 °C until the time of analysis, and d-ROM and BAP were measured within 48 h after blood collection. The samples obtained right after surgery and on the first POD were drawn from the radial arterial line, which was removed after blood collection. The blood samples at other time points were obtained from a peripheral vein.

### Statistical Analysis

The results for continuous variables are reported as the mean or median, and the results for categorical variables are reported as the number (percentage) of patients. A Chi-square test was used compare categorical data between groups. When measurements were repeated over time, the data were analyzed by a two-way factorial analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant. All analysis was performed with SAS (ver. 9.2) (SAS Institute, Tokyo, Japan).

## Results

All 32 patients underwent pulmonary resection for primary NSCLC, with nineteen cases of lobectomy, eight cases of segmentectomy, and five cases of partial resection. Patients were divided into two groups according to the type of thoracotomy. Seventeen patients had a thoracotomy using metal retractors (thoracotomy group), while fifteen patients had video-assisted thoracic surgery (VATS group). Age (68 vs 70 years old,  $p=0.39$ ), gender (Male / Female: 10/5 vs 10/7 patients,  $p=0.68$ ), preoperative carcinoembryonic antigen (CEA: 2.9 vs 3.9 ng/ml,  $p=0.78$ ), the coexistence of diabetes needed hypoglycemic medication or insulin (1 vs 1 patient,  $p=0.52$ ), operation time (218 vs 230 minutes,

$p=0.63$ ), blood loss (120 vs 100ml,  $p=0.17$ ), and the distribution of pathological stage of cancer did not significantly differ between the two groups ( $p=0.28$ ). However, the type of histology (Adenocarcinoma / squamous cell carcinoma,  $p<0.02$ ) and the operative procedure (either lobectomy / limited resection, including segmentectomy and partial resection, (6/9, 13/4 cases,  $p<0.04$ ) were significantly different between the two groups. The patient profiles of both groups are shown in Table 2. One patient in the thoracotomy group experienced severe pyothorax after the study period, and two patients had pneumonia in each group, and prolonged air leakage was seen in one patient whose chest tube was removed after postoperative day 11 in thoracotomy group. No drug-related adverse effect or complications were caused by the analgesic procedures.

The average preoperative d-ROM and BAP levels in all patients were 322 U.CARR (median, 308; range, 127-578) and 2069  $\mu\text{mol/L}$  (median, 2019; range, 413-3467), respectively. The d-ROM level right after surgery (184 U.CARR) and on the first POD (254 U.CARR) significantly decreased compared with the preoperative values ( $p<0.0001$  for both). However, the d-ROM level recovered by the third POD to the preoperative level. A similar fluctuation was seen in the BAP level. The BAP level significantly decreased right after surgery (1541 U.CARR) compared with preoperative level ( $p<0.0006$ ). Then, the BAP level recovered on the first POD to the preoperative level (Fig. 1).

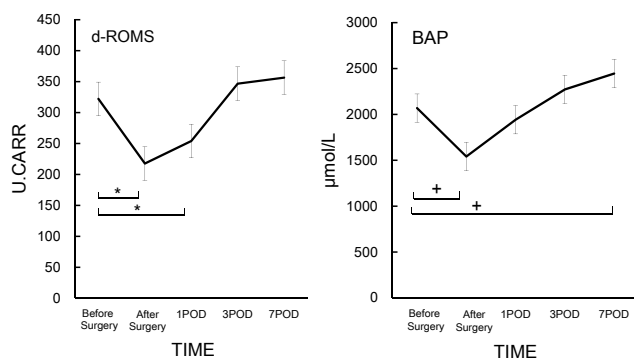
The average d-ROM level in the VATS group was significantly lower than that in the thoracotomy group on the third POD (313 vs 385 U.CARR,  $p<0.04$ ). The average BAP level in the VATS group was significantly less than that in the thoracotomy group right before surgery and on the third POD (1397 vs 1705  $\mu\text{mol/L}$ ,  $p<0.009$ ; 2088 vs 2481  $\mu\text{mol/L}$ ,  $p<0.03$ ; respectively) (Fig. 2).

**Table 2.** Patient profiles in the two groups

Variable	Thoracotomy group	VATS group	p-value
Number	17	15	
Age (median)	68	70	0.39
Male / Female	10 - 5	10 - 7	0.68
Adeno / Squamous	9 - 6	16 - 1	0.02
CEA (median)	2.9	3.9	0.78
Diabetes	1	1	0.52
Lobectomy / Limited	6 - 9	13 - 4	0.04
Operation time (median, min)	218	230	0.63
Blood loss (median, ml)	120	100	0.17
Pathological stage (I/II/III/IV)	11-2-2-0	15-0-1-1	0.28

CEA: carcinoembryonic antigen; VATS: video-assisted thoracic surgery

#### Perioperative changes of d-ROM and BAP in all patients



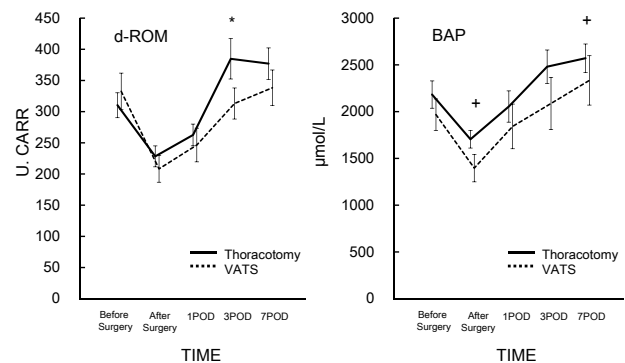
**Figure 1.** Perioperative changes in d-ROM and BAP levels in all patients

For d-ROM, the level was significantly higher on the third postoperative day ( $p < 0.0001$ ). However, the level recovered and remained within the moderate stress range (Table 1). The BAP level was significantly decreased on the first postoperative day ( $p < 0.0006$ ). Moreover, the level recovered and remained within the normal range (Table 1).

d-ROM: diacron reactive oxygen metabolites; BAP: biological antioxidant potential

POD: postoperative day

#### Perioperative changes of d-ROM and BAP in Thoracotomy group and VATS group



**Figure 2.** Perioperative changes in d-ROM and BAP levels in the thoracotomy and VATS groups

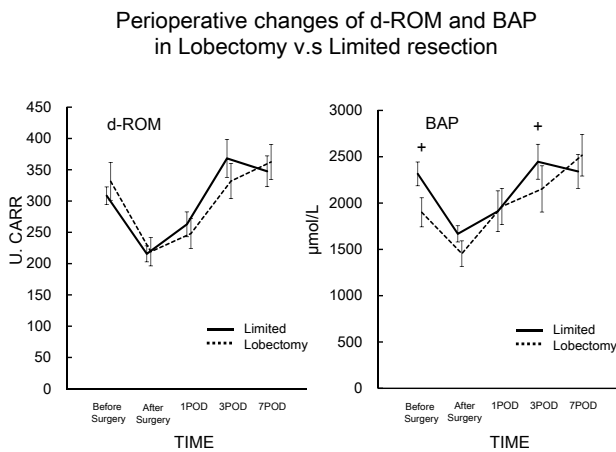
In general, the changes in d-ROM and BAP over time after both procedures were similar. The d-ROM level in the thoracotomy group was significantly higher than that in VATS group on the third postoperative day ( $p < 0.04$ ). The BAP level in the thoracotomy group was significantly higher than that in VATS group right after surgery ( $p < 0.009$ ) and on the third postoperative day ( $p < 0.03$ ).

d-ROM: diacron reactive oxygen metabolites. BAP: biological antioxidant potential

POD: postoperative day

Since there was a significant difference in the type of procedure (lobectomy vs limited resection) between the VATS and thoracotomy groups, we also compared the d-ROM and BAP levels between the lobectomy and limited resection groups. The d-ROM level was not significantly different be-

tween the lobectomy and limited resection groups. The BAP level in the limited resection group was significantly greater than that in the lobectomy group on the third POD (2446 vs 2153  $\mu\text{mol/L}$ ,  $p < 0.01$ ) (Fig. 3).



**Figure 3.** Perioperative changes in d-ROM and BAP levels in the lobectomy and limited resection groups

In general, the changes in d-ROM and BAP over time after both procedures were similar. The d-ROM levels in the lobectomy group and limited resection group were not significantly different. The BAP level in the limited resection group was significantly higher than that in lobectomy group before surgery ( $p < 0.02$ ) and on the third postoperative day ( $p < 0.01$ ).

d-ROM: diacron reactive oxygen metabolites, BAP: biological antioxidant potential

POD: postoperative day

## Discussion

We evaluated perioperative oxidative stress in lung cancer patients using a Free Radical Elective Evaluator and obtained three important findings. First, lung cancer patients already had increased oxidative stress before surgery. Second, the level of oxidative stress and antioxidant potential was markedly altered by surgical stress. Third, VATS attenuated perioperative oxidative stress response compared with standard thoracotomy.

Oxidative stress can be defined as an imbalance between the pro-oxidant and the antioxidant potential of cells, which results either from an overproduction of ROS, insufficient detoxification of ROS by antioxidants, or a combination of both [1]. This imbalance leads to a state of oxidative stress that contributes to the pathogenesis of several human diseases. For instance, it is generally accepted that cigarette smoke is an important determinant of carcinogenesis. Cigarette smoke contains free radicals and induces oxidative stress that may be involved in cancer development [14]. Additionally, it is widely known that reperfusion injury after cardiopulmonary bypass (CPB) is accompanied by structural damage due to the interactions of free radicals, endothelial factors, and neutrophils [2, 7, 8, 15-17]. The lung is a critical

organ in mediating an increase of oxidative stress of either systemic or pulmonary origin, because the pulmonary parenchyma is one of the largest reservoirs for neutrophils, monocytes, and macrophages. Therefore, we became interested in perioperative oxidative stress in lung cancer patients.

Gencer et al. [18] evaluated the d-ROM level in different histopathological types of lung cancer, including small cell carcinoma (SCLC), adenocarcinoma, and epidermoid carcinoma. They found that the d-ROM in all types of lung cancer was significantly increased compared with healthy volunteers, and the value was highest in SCLC. In our study, the median d-ROM in all patients was 322 U.CARR, which indicates the existence of slight oxidative stress before surgery. However, we could not evaluate the correlation between oxidative stress and histological types because we did not take the smoking history of patients into consideration, and the number of patients was limited. Tsukioka et al. [4] found that an increase in preoperative d-ROM indicates nodal extension in patients with clinical stage I lung adenocarcinoma. In that study, patients with a d-ROM above 318 U.CARR were likely to develop nodal status. According to these reports and our results, it appears that the measurement of d-ROM level in lung cancer can reflect cancer progression.

It seems reasonable that lung cancer surgery causes stress to the human body, and this is increased even more by single-lung ventilation, which imposes an excessive burden on the contralateral lung. In fact, Misthos et al. [11] reported that protracted single-lung ventilation should be considered a potential cause of cardiovascular complications through the generation of severe oxidative stress due to lung re-expansion. In that study, the plasma malondialdehyde level was used as an index of lipid peroxidation. Kanaoka et al. [2] monitored d-ROM and BAP levels during cardiovascular surgery with and without CPB. The d-ROM level increased gradually after surgery for up to 2 weeks; moreover, the d-ROM level after surgery that required CPB became higher than that in the group without CPB. Our results showed that the d-ROM level decreased shortly after surgery but then increased back to the preoperative levels. There are several reports that d-ROM levels normalize perioperatively or within 1 to 2 days postoperatively [15, 16]. From these points, general anesthesia itself could cause oxidative stress. However, in this study, the type of general anesthesia was uniformed by using propofol and rocuronium. In addition, as we have shown in table 2, the operation time and blood loss was not significantly different between VATS and Thoracotomy. So we could not conclude that d-ROM depended on the anesthesia.

On the other hand, Tsuchiya et al. [5] measured levels of d-ROM and BAP during sigmoidectomy under several conditions (laparoscopic vs open and sevoflurane vs propofol). They reported that only d-ROM decreased significantly at the end of surgery for both open sigmoidectomy and laparoscopic sigmoidectomy under propofol anesthesia. They concluded that propofol anesthesia directly reduced hydroperoxides by functioning as an antioxidant. Therefore, propofol anesthesia in our study might also have contributed to the reduction of the d-ROM level shortly after surgery.

Although d-ROM was decreased shortly after surgery in the present study, we also observed a transient decrease in the BAP level. There are some reports in which the antioxidant potential decreased during surgery, especially during aortic clamping and after declamping, which was interpreted as an increase in oxidative stress [2, 7, 8]. It has been reported that after ROS are eliminated, the antioxidant level immediately recovers to the normal level by the antioxidant recycling pathway [19]. Therefore, we also speculated that immediate BAP recruitment occurred for compensation of the oxidative stress that occurred during the acute postoperative phase resulting in a significant decrease in both d-ROM and BAP right after surgery.

Currently, VATS is widely accepted and used for most thoracic surgeries, given the reduced invasiveness and equivalent or favorable surgical results compared with conventional thoracotomy [20]. Moreover, we previously demonstrated that VATS decreased the post-thoracotomy pain syndrome compared with conventional thoracotomy [12]. Although Tsuchiya et al. [5] reported that a laparoscopic procedure (sigmoidectomy) was not associated with intraoperative oxidative stress, there have been no reports on perioperative oxidative stress based on the type of thoracotomy. In our study, the d-ROM level in the VATS group was significantly less than that in the thoracotomy group on the third postoperative day (313 vs 385 U.CARR,  $p < 0.04$ ). This finding confirmed that VATS caused less oxidative stress compared with standard thoracotomy. As shown in Fig. 3, d-ROM levels in both lobectomy and limited resection (partial resection and segmentectomy) were not significantly different. We speculated that most cases of limited resection were done by thoracotomy in our study, because of the need for a secure surgical margin and the technical difficulty, especially for VATS segmentectomy. Additionally, post-thoracotomy pain also could influence these results, because Kim et al. [9] reported that ROS played an important role in a rat model of neuropathic pain.

The present study had two main limitations. First, the sample population was small and obtained from a single in-

stitution, and small samples may affect the accuracy of the statistical analysis. Second, the patient characteristics were different, including clinical stage, histology, and surgical procedures. Moreover, we did not consider several other factors that might affect oxidative stress, such as smoking, hyperlipidemia, and dietary consumption of antioxidants, and these factors might have influenced the d-ROM and BAP levels. Future studies are needed to address these limitations and to determine whether decreased perioperative oxidative stress has a significant impact on the clinical course of lung cancer patients, as reported previously [11]. In the future, less invasiveness of surgery including port reduced surgery and robotic surgery will be evaluated by measurement of d-ROM. In addition, the d-ROM could be measured among transplanted patients to identify allograft rejection or infection. Thus, the measurement of d-ROM will be promising methods among various surgical fields.

In conclusion, to the best of our knowledge, this is the first study to assess perioperative oxidative stress using d-ROM and BAP in lung cancer surgery. The coexistence of lung cancer and the surgical procedure generates ROS. The present study also demonstrated that VATS suppressed perioperative oxidative stress compared with standard thoracotomy. In the future, accumulation of clinical cases is needed because this study had limited the number of patients.

**Acknowledgments:** none

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