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Cardiopulmonary and Oxidative Stress Effects of Lung Lobectomy in Dogs; Comparison of Open and Thoracoscopic Surgery

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Abstract : In the present study, we investigated and compared the cardiopulmonary and oxidative stress effects of dogs undergoing open and thoracoscopic lung lobectomy. Ten healthy dogs, 5-8 years old, weighing 9-12 kg were used. The animals were randomly assigned to one of two groups according to the type of surgical procedure; open (group 1, n = 5) or thoracoscopic lung lobectomy (group 2, n = 5). Cardiopulmonary parameters, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) concentrations were measured. There were statistically significant changes in arterial blood gases values in both groups. Total anesthesia and surgical times were significantly shorter in thoracoscopic lobectomy group compared with open surgery group. Increases in plasma SOD and CAT levels, and decreases in GPx levels were observed in both groups after surgery. Significant difference in GPx levels was found when the groups were compared. The GPx level was significantly lower in the thoracoscopic lobectomy group compared with the open surgery group.

***Key words* :** thoracoscopic lung lobectomy, cardiopulmonary effect, oxidative stress, dogs.

Introduction

A lobectomy, also called pulmonary lobectomy or lung lobectomy, is the surgical removal of a lobe of the lung. It is done to remove a portion of diseased lung, such as early stage lung cancer. Video assisted thoracosopic surgery, often referred to as VATS, is a surgical method in which the surgery is performed using a small camera that is introduced into the patient's chest via a scope. Utilizing the camera the surgeon can view the anatomy and with other surgical instruments, that are introduced into the chest via small incisions or "ports" the surgical problem can be addressed. VATS is routinely performed as a diagnostic and therapeutic procedure in humans (8,12,17). When compared with thoracotomy, similar procedures performed using thoracoscopy in humans result in reduced chest wall trauma and deformity, reduced postoperative pain, decreased patient morbidity, and shorter hospitslization stay (8). Thoracoscopy has been used in dogs for biopsy of lung, mediastinum and pleura, treatment of persistent right aortic arch, identification and ligation of the thoracic duct, pericardiectomy, and occlusion of patent ductus arteriosus (1,2,4,9,11,17,19).

Oxidative stress in the body represents an imbalance between the production of reactive oxygen species (ROS) and the ability of the antioxidant defence mechanisms to detoxify the reactive intermediates. An excess of ROS can damage all cellular components, including proteins, lipids, and nucleic acids. Although lung lobectomy with thoracoscopy has been reported in healthy dogs, no controlled studies have been conducted to evaluate oxidant-antioxidant status of thoracoscopic surgery in dogs. In the present clinical study, we investigated and compared the oxidant-antioxidant status of dogs undergoing open and thoracoscopic lung lobectomy.

Materials and Methods

Animals and anesthesia

Ten healthy dogs, 5-8 years old, weighing 9-12 kg were used. All dogs were healthy based on clinical examinations. The experimental and housing protocols were approved by the Chungnam National University Animal Care and Use Committee (approval no. CNU-00178). This study was conducted 14 days after procuring the dogs. The dogs were kept in a quiet room to avoid any stress-inducing factors during this period. Food was withheld for 8-12 h prior to anesthesia, but access to water was allowed. The animals were randomly assigned to one of two groups according to the type of surgical procedure; open (group 1, n = 5) or thoracoscopic lung lobectomy (group 2, n = 5).

The dogs were premedicated with atropine sulfate ((0.04 mg/kg, SC: Atropine Sufate Injection®, Daihan Pharm), cefazoline (20 mg/kg, IV: Falexin®, Dong Wha Pharm, Seoul, Korea) and an analgesic agent, butorphanol (0.2 mg/kg, IM:

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Butophan Injection®, Myungmoon Pharm) before the induction of anesthesia. Anesthesia was induced with propofol (4 to 6 mg/kg: Aanepol Injection®, Hana Pharm) and 100% oxygen. After endotracheal intubation, anesthesia was maintained with isoflurane (Forane Sol®, Choongwae Pharm, Seoul, Korea), at an end-tidal concentration of 2%, using a Datex ohmeda ADU anesthesia system (Helsinki, Finland), with an oxygen flow rate of 2 L/min. Heart rate, mean arterial pressure, end-tidal carbon dioxide, peripheral oxygen saturation, and respiratory rates were measured. Arterial blood samples were collected anaerobically and analyzed immediately using a portable analyzer (i-STAT; Portable Clinical Analyzer, Heska). The analyzer calculated sample arterial oxygen partial pressure (P_aO_2), carbon dioxide partial pressure (P_aCO_2), arterial oxygen saturation (S_aO_2), total amount of CO_2 (TCO_2), concentration of hydrogen carbonate (HCO_3) and arterial pH.

During the anesthesia, the dogs were given IV fluid (Hartmann's solution, 10 ml/kg/h).

In addition, local intercostals bupivacaine was administered to the dog at total dose of 1.5 mg/kg divided between cannula sites at skin closure.

Open surgery

A lateral intercostals thoracotomy was performed at the level of the fourth intercostals space. A 5-7 cm long incision was made at the ventral third of the 5th intercostals space that included all layers of the thoracic wall through the intercostals muscles. The pleural incision was made during exhalation by using Metzembaum scissors. The scissors were left open in the incision for 2 min to allow air to enter the pleural cavity and collapse the lung. Total lung lobectomy of the right middle lobe was performed using an automatic stapling equipment (45 mm long cartridges and 3.5 mm staples, EndoGIA stapler). The stapler was placed across the hilus of the lung, to exclude vessels and tissue of other lobes for sure. After the stapler was opened, the lung lobe was released and checked for hemorrhage or leakage. A thoracostomy drain was placed to establish negative pressure in the pleural space before closing the incision. The intercostal incision was closed by placing circumcostal sutures of 1-0 absorbable material to approximate the ribs. Each muscle layer, subcutaneous tissue and skin was closed with continuous patterns.

Thoracoscopic surgery

Thoracoscpic surgery was performed through intercostal approach. Three cannulas (one 12 mm and two 5 mm cannulas, Ethicon Disposable rigid trocars, Ethicon Endosurgery Inc., Cincinnati, OH) were placed the 4th, 8th and 10th intercostal spaces. The skin was incised to a size equivalent to cannular diameter. The thoracic wall was bluntly dissected with a mosquito forceps until the thoracic cavity was perforated. For resection of middle lobes, the cannular for the camera was inserted in the ventral aspect of the 8th intercostal space. One instrument cannula was inserted dorsally in the 10th intercostal space and a 2nd instrument cannular was inserted in the 4th intercostal space to gain access to the middle lung lobe. Lobectomy was achieved using a 45 mm EndoGIA stapler with 3.5 mm cartridges (EndoGIA, United States Surgical Corporation, Tyco Healthcare Group Norwalk, CT). Resected lobes were placed an endoscopic retrieval bag (Endobag, United States Surgical Corporation). Lobes were removed through an extended incision of 1 instrument portal without retraction of ribs in dogs that did not require thoracotomy. A chest tube was placed in a routine manner from dorsal to ventral, caudal to cranial traveling over 3 intercostals spaces, avoiding cannula sites in all dogs.

Monitoring and postoperative care

Vital signs were monitored continuously during surgery. Total anesthesia and surgical times were recorded for each dog. Total anesthesia time was the time from the injection of propofol to when dogs achieved sternal recumbency. Total surgical time was the time from the first port placement (thoracoscopic group) or skin incision with blade (open group) to the time that the port sites (thoracoscopic group) or skin layers (open group) were closed. Blood samples were obtained for arterial blood gases analysis before anesthesia and the end of surgery. After surgery, each animal was monitored until they were ambulatory. Dogs were given butorphanol 0.2 mg/kg intramuscularly at the end of the surgical procedure for postoperative analgesia. A second dose of butorphanol 0.1 mg/kg was given intramuscularly 6 h after surgery. Water and moistened dog food were offered 12 h after surgery.

Oxidative stress parameters

Approximately 3 ml blood was collected into a plasma separation tube containing heparin for analysis of oxidative stress markers. Blood samples were centrifuged at 3000 rpm for 10 min to separate plasma, and the plasma samples were stored at −80ºC until analysis. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) concentrations were measured with a commercial kit (Cayman Chemical Company, Ann Arbor, MI, USA) using a spectrophotometer (Bio-Tek Instruments, Winooski, VT, USA).

Statistical analysis

All statistical analyses were performed using SPSS version 19.0 (Chicago, IL, USA). Results are expressed as mean ± SD. A Mann-Whitney *U*-test was applied with a $p\text{-value} < 0.05$ being considered significant.

Results

All dogs were hemodynamically stable during anesthesia and surgery (Table 1). There was no significant worsening in vital signs. There were statistically significant changes in arterial blood gases values in both groups (Table 2). P_aO_2 and lactate were significantly lower in thoracoscopic surgery group compared with open surgery group. Total anesthesia and surgical time were significantly shorter in thoracoscopic lobec-

Table 1. Heart rate (HR), respiratory rate (RR), mean arterial blood pressure (MAP), rectal temperature (RT), pulse oximeter oxygen saturation (SpO_2), end-tidal CO_2 ($ETCO_2$) and tidal volume (TV) in dogs undergoing open or thoracoscopic lung lobectomy

	Group	Pre	10 min	20 min	30 min	40 min	50min
HR	Open	131 ± 16	127 ± 20	119 ± 10	113 ± 16	136 ± 15	141 ± 15
(beats/minutes)	Thoracoscopy	131 ± 20	119 ± 18	116 ± 28	113 ± 11	118 ± 16	128 ± 14
RR	Open	22 ± 6	21 ± 7	16 ± 7	25 ± 14	26 ± 12	25 ± 13
(beats/minutes)	Thoracoscopy	22 ± 5	19 ± 5	24 ± 10	21 ± 10	22 ± 8	24 ± 5
MAP	Open	74 ± 13	61 ± 11	81 ± 22	63 ± 11	61 ± 8	67 ± 16
(mmHg)	Thoracoscopy	77 ± 16	73 ± 18	81 ± 18	89 ± 17	80 ± 10	87 ± 11
RT	Open	38.1 ± 0.7	37.9 ± 0.4	37.8 ± 0.4	37.6 ± 0.5*	37.5 ± 0.6*	37.4 ± 0.4*
(°C)	Thoracoscopy	38.4 ± 0.5	38.2 ± 0.6	38.1 ± 0.6	38.1 ± 0.5	38.0 ± 0.5	37.8 ± 0.7*
S_aO_2	Open	94 ± 1	95 ± 2	96 ± 3	94 ± 2	96 ± 1	96 ± 2
(%)	Thoracoscopy	97 ± 1	96 ± 2	95 ± 1	94 ± 1	95 ± 2	96 ± 2
$ETCO_2$	Open	46 ± 3	47 ± 7	44 ± 8	45 ± 3	44 ± 9	45 ± 6
(mm Hg)	Thoracoscopy	42 ± 3	39 ± 5	44 ± 8	45 ± 5	46 ± 7	46 ± 6
TV	Open	93.8 ± 46.4	97.2 ± 43.2	81.8 ± 8.0	103.0 ± 62.7	81.4 ± 41.2	96.6 ± 27.6
(ml)	Thoracoscopy	95.8 ± 16.7	65.4 ± 19.1*	57.3 ± 33.1*	78.9 ± 13.5	95.3 ± 22.5	96.9 ± 25.7

Data are expressed as the mean ± SD (n = 5). Open, open lung lobectomy group; Thoracoscopy, thoracoscopic lung lobectomy group.
*Significantly different ($P < 0.05$) from the baseline.

Table 2. Blood gases data in dogs undergoing open or thoracoscopic lung lobectomy

Parameters	Group	Preoperative	Postoperative	P
PCO_2	Open	45.4 ± 5.31	60.7 ± 6.67	0.002*
(mm Hg)	Thoracoscopy	43.2 ± 3.68	60.16 ± 7.40	0.002*
PaO_2	Open	478.6 ± 47.26	327.3 ± 58.84	0.03*
(mm Hg)	Thoracoscopy	455.6 ± 68.43	237.3 ± 88.86	0.03*, 0.04**
SaO_2	Open	100 ± 0	98 ± 2.7	NS
(mm Hg)	Thoracoscopy	100 ± 0	97 ± 3.1	NS
pH	Open	7.35 ± 0.04	7.21 ± 0.03	NS
	Thoracoscopy	7.32 ± 0.05	7.18 ± 0.06	0.03*
TCO_2	Open	25.6 ± 1.51	26.2 ± 3.03	NS
(mm Hg)	Thoracoscopy	23.6 ± 1.14	24.2 ± 1.30	NS
HCO_3	Open	24.0 ± 1.5	23.7 ± 2.7	NS
(mEq/L)	Thoracoscopy	22.0 ± 1.2	22.4 ± 1.31	NS
Lactate	Open	1.02 ± 0.40	1.48 ± 1.23	NS
(mmol/L)	Thoracoscopy	0.71 ± 0.25	0.9 ± 0.30	0.04**

Mean ± SD Open, open lung lobectomy group; Thoracoscopy, thoracoscopic lung lobectomy group. PCO_2, carbon dioxide partial pressure; PaO_2, arterial oxygen pressure; SaO_2, arterial oxygen saturation; TCO_2, total amount of CO_2; HCO_3, concentration of hydrogen carbonate. NS, not significant.
*Statistically difference ($P < 0.05$) compared to "preoperative" (n = 5).
**Statistically difference ($P < 0.05$) compared to open surgery group (n = 5).

tomy group compared with open surgery group (Fig 1). Increases in plasma SOD and CAT levels, and decreases in GPx levels were observed in both groups after surgery (Fig 2). Significant difference in GPx levels was found when the groups were compared. The GPx level was significantly lower in the thoracoscopic lobectomy group compare with the open surgery group.

Discussion

Surgery results in a wide spectrum of unfavorable alterations in normal body homeostasis, which are caused the oxidative stress. The increase in the production of ROS due to surgical stress has been reported and it's known that surgical trauma causes an increase in free radical production (15).

Thoracoscopic lung resection without conversion to thora-

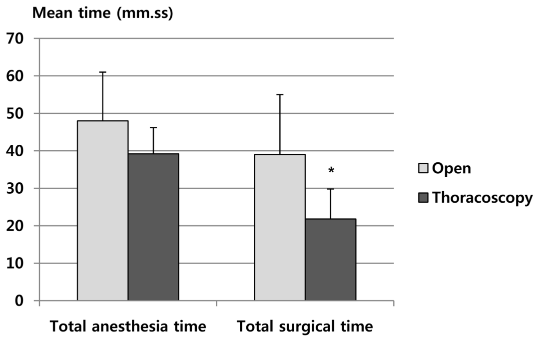

Fig 1. Total anesthesia and total surgical time in dogs. Data are expressed as mean ± SD (n = 5). Open, open lung lobectomy group; Thoracoscopy, thoracoscopic lung lobectomy group. *Statistically difference ($P < 0.05$) compared to open surgery group (n = 5).

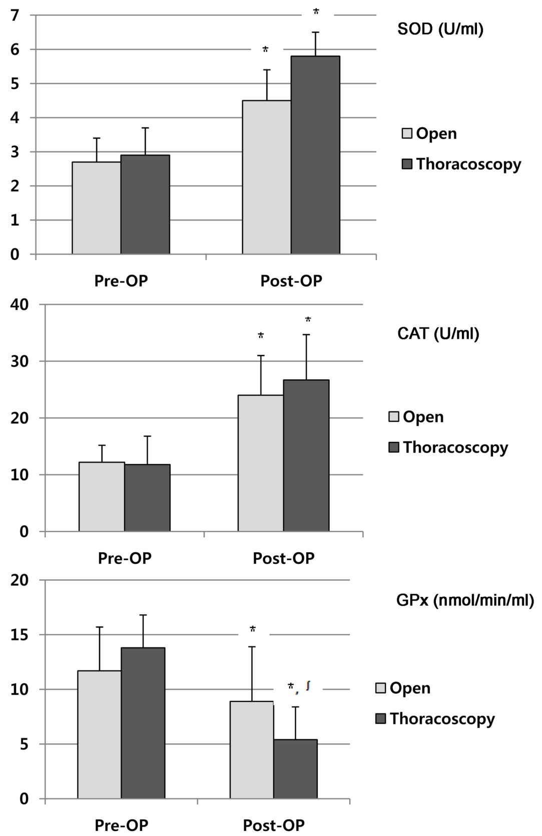

Fig 2. Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) data in dogs. Data are expressed as the mean ± SD (n = 5). Open, open lung lobectomy group; Thoracoscopy, thoracoscopic lung lobectomy group. Pre-OP; pre-operation, Post-OP; post-operation. *Significantly different ($P < 0.05$) from baseline. Significantly different ($p < 0.05$) from Open.

cotomy was accomplished in dogs. Right middle lobe was removed successfully by thoracoscopy without intraoperative complication.

Lung lobectomy is indicated for treatment of primary or metastatic lung neoplasia, bullae/bleb formation, chronic consolidation, major trauma, pulmonary abscessation, or lung lobe torsion. Traditionally, the approach to lobectomy has been via either intercostal thoracotomy or median sternotomy. In veterinary medicine, both thoracoscopic-assisted and totally thoracoscopic techniques have been described for lung lobectomy. Intercostals thoracotomy has been the traditional surgical approach for gaining access to the thoracic cavity. However, this procedure is associated with considerable postoperative morbidity including pain, seroma development, incisional dehiscence, and pulmonary dysfunction (3,6,16,18). Extensive skin incisions, subcutaneous tissue and muscle dissection, followed by rib retraction all contribute to the postoperative pain and morbidity associated with open thoracic procedures.

In general, the thoracoscopic-assisted techniques may be used in cases in which the thoracic mass is modestly size and located somewhat peripherally within the lobe and requires larger thoracic wall incisions to safely exteriorize the affected lobe. The totally thoracoscopic technique allows resection of somewhat lager masses closer to the hilum, although the easiest cases involve masses that are modestly size and peripheral (13).

Previous study, poor access occurred only for the right middle lobe and thoracoscopic removal of this lobe has not been successfully performed in dogs (7). They found that placement of the cannulae did not provide enough working space to manipulate the instruments and the middle lobe for safe application of staples at the hilus. However, the placement of the three cannulae provided enough working space to procedure in this study. In additions, in most cases that require a totally thoracoscopic partial or complete lobectomy, one-lung ventilation is mandatory to provide adequate visualization of the pulmonary hilum. However, in this study, thoracoscopic lung lobectomy can be performed without the use of one-lung ventilation. Although the thoracic wall was intact with thoracoscopy, the change in compliance and the alteration of intrapulmonary gas distribution was higher than those occurring during open thoracotomy. In this study, the blood gases parameters significantly affected by open surgery were PCO_2 and PaO_2. In contrast to open thoracotomy, the blood gases parameters significantly affected by thoracoscopic surgery were PaO_2 and Lactate.

Oxidative stress in the body represents an imbalance between the production of reactive oxygen species (ROS) and the ability of the antioxidant defense mechanisms to detoxify the reactive intermediates (14). The greater the oxidative stress, the more severe the resulting cellular damage during surgery may cause poor outcome in patients (14), and the minimization of oxidative stress is therefore very important. The blood contains many antioxidant molecules that prevent and inhibit the harmful effects of ROS. The main enzymes that control the biological effects of ROS are SOD, CAT and GPx. SOD catalyses dismutation of the superoxide anion into H_2O_2; CAT detoxifies H_2O_2; GPx oxidizes reduced glutathione, inactivates H_2O_2, and reduces organic peroxides to their alcohols (10). These antioxidant enzymes respond to increased oxidative stress and act as ROS scavengers. Therefore, measuring antioxidant enzymes activities reflects the antioxidative status of the antioxidant defense system.

In this study, the results show that dogs underwent thoracoscopic or open lung lobectomy had decreased GPx activity and increased SOD and CAT activities in erythrocytes. Increased SOD and CAT activities due to the effect of free radicals formed with surgical trauma. Decreased GPx activity reflects the consumption of GPx due to oxidative stress. Trauma and surgical injury are associated with increased production of ROS, and the use of antioxidant system, in particular when associated with relative tissue ischemia followed by reperfusion, may inhibit ROS production. A recent study reported that surgical trauma alone raises oxidative stress (5). In a similar manner, in this study, the activities of antioxidant enzyme were increased after surgery.

The goals of surgical treatment of lung masses in dogs are similar to those in human surgery: an effective procedure, decreased postoperative morbidity, and rapid return to normal activity. In this study, changes in oxidative stress parameters were evident during open or thoracoscopic lobectomy in dogs. Less change of enzyme activities was observed in open surgery group compared with thoracoscopic surgery group. In addition, total anesthesia and surgical times were shorter in thoracoscopic surgery compared with open surgery.

In conclusions, thoracoscopic lung lobectomy provided a less invasive, simpler, and faster surgical times for lung lobectomy in dogs. However, thoracoscopic surgery has more detrimental effect on cardiopulmonary and oxidative stress status compared with open surgery. Further studies are required to evaluate the efficacy of thoracoscopic lung lobectomy in dogs.

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개에서 폐엽절제가 심폐기능 및 산화 스트레스 상태에 미치는 영향; 일반개흉 및 흉강경을 통한 폐엽절제술 비교

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요 약 : 본 연구에서는 개에서 일반 개흉술을 통한 폐엽절제술과 흉강경을 이용한 폐엽절제술에서 심폐기능 및 생체 내 산화스트레스 상태에 미치는 영향을 비교 연구 하였다. 10 마리의 건강한 혼혈종을 사용하였고 일반 개흉술을 통한 폐엽절제술군 (group 1, n = 5)과 흉강경을 이용한 폐엽절제술군 (group 2, n = 5)으로 분류하였다. 심혈관계 측정 항목 및 superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx)의 농도를 측정하였다. 두 군에서 동맥혈액 가스의 유의적인 변화를 관찰 할 수 있었다. 총 마취 및 수술 시간은 개흉수술군에 비해 흉강경 폐엽 절제술군에서 유의하게 짧았다. 혈장 SOD와 CAT 수준의 증가, 그리고 GPX 수준의 감소는 수술 후 두 군 모두에서 관찰되었다. 두 군을 비교했을 때 GPX 수준에서 유의한 차이가 발견되었다. GPX 수준은 개흉 수술 군과 비교 흉강경 폐엽 절제술 군에서 유의하게 낮았다.

주요어 : 흉강경 폐엽절제 수술, 심폐 영향, 산화 스트레스, 개.