Sevoflurane did not show better protective effect on endothelial glycocalyx layer compared to propofol during lung resection surgery with one lung ventilation

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**Background:** The endothelial glycocalyx layer (EGL) coats the alveolar capillary endothelium and plays important roles in pulmonary vascular protection, modulation, and hemostasis. Ischemia-reperfusion, which occurs during lung resection surgery with one lung ventilation (OLV), can damage the EGL. Sevoflurane is known for its protective effect against ischemia-reperfusion injury. Therefore, we hypothesized that lung resection surgery produces EGL damage and sevoflurane protects the EGL better than the intravenous anesthetic propofol.

**Methods:** Seventy-eight patients undergoing pulmonary resection were randomly allocated into the sevoflurane (n=38) and propofol (n=40) groups. All patients received OLV and protective ventilation under sevoflurane- or propofol-based anesthesia. The concentrations of EGL injury markers (heparan sulfate and human syndecan-1) and an inflammatory marker (vascular cell adhesion molecule-1) were measured from blood samples drawn at five time points (after induction, 60 min after OLV, 120 min after OLV, end of OLV, and end of surgery).

**Results:** OLV increased the concentrations of EGL injury markers; heparan sulfate concentrations increased from 120 minutes after OLV (120 minutes after OLV: sevoflurane, 13.3±6.8 ng/mL, P<0.05; propofol, 14.8±6.9 ng/mL, P<0.05). Human syndecan-1 concentrations also increased from 120 minutes after OLV (120 minutes after OLV: sevoflurane, 20.4±8.9 ng/mL, P<0.05; propofol, 20.5±11.8 ng/mL, P>0.05). However, no difference in EGL injury markers was observed between the sevoflurane and propofol groups at any time point. Vascular cell adhesion molecule-1 concentrations did not show any temporal changes in either group.

**Conclusions:** Lung resection surgery with OLV produced EGL damage without any increase in inflammation. Although shedding of heparan sulfate induced by EGL injury during lung resection surgery with OLV, was less than propofol, it was not statistically significant.

**Keywords:** Glycocalyx; lung resection surgery; one lung ventilation (OLV); sevoflurane; propofol

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Introduction

Advances in surgical techniques, anesthetics, anesthetic methods, and critical care have led to a decline in morbidity and mortality after pneumonectomy. However, acute lung injury (ALI) after pneumonectomy is still a dangerous and fatal complication (1) with an incidence ranging between 3% and 10% (2,3).

Factors known to contribute to ALI include surgical trauma, overhydration (3), and one lung ventilation (OLV) (4). In particular, OLV may cause ALI through ventilation-induced injury in the ventilated lung and ischemia-reperfusion injury in the collapsed lung (5).

The endothelial glycocalyx layer (EGL) is a multicomponent layer, comprising glycoprotein and proteoglycan, at the luminal surface of the vascular endothelium (6). EGL plays an important role in tissue fluid balance and edema formation, and has a critical role in maintaining vascular homeostasis (7). EGL injury is an important cause of pulmonary edema during ALI through inflammatory responses, capillary leakage, and edema formation (8). Patients who incur lung injury after pneumonectomy show high pleural fluid protein levels, suggesting they have elevated endothelial permeability, thereby indicating EGL injury.

Despite growing interest on the EGL, no reports have documented EGL injury in relation to lung resection surgery with OLV. Therefore, we aimed to investigate whether lung resection surgery with OLV leads to EGL injury by examining the blood concentrations of EGL components, namely heparan sulfate and human syndecan-1. In addition, we measured the concentrations of vascular cell adhesion molecule-1 (VCAM1) as an indicator of inflammation.

In previous human studies or animal experiments, we measured the damage of EGL resulting from cardiac surgery, trauma patients or transplantation through blood sampling, and the authors also measured this using blood sampling. The most accurate method was to use bronchoalveolar-lavage, but it was not appropriate in patients with pulmonary resection and could not be selected (9-11).

In general, the choice of anesthetics for pneumonectomy has been discussed in relation to hypoxic pulmonary vasoconstriction, but recently, studies have examined the inhibition of inflammatory factors in relation to ALI (12). Recent studies have reported that sevoflurane, an inhalational anesthetic, protects the EGL from ischemia-reperfusion injury (13) by reducing the adhesion of leukocytes and platelets to the vascular endothelium (14).

Another mechanism seems to sevoflurane attenuate lysosomal cathepsin B releasing and to be independent from tissue mast cell degranulation (15). Hence, we investigated whether sevoflurane was superior to propofol in reducing EGL injury during lung resection surgery with OLV.

Our hypothesis was that lung resection surgery with OLV produces EGL damage and sevoflurane protects the EGL better than the intravenous anesthetic propofol does.

Methods

Patient selection

This study was approved by the hospital’s institutional ethics committee (No. PNUYH 05-2014-098), and informed consents were obtained from the patients the day before surgery. Eighty-seven patients with American Anesthesiology Association physical status 1 and 2 who were scheduled to undergo lung resection surgery with OLV were enrolled in this study. Patients who had a history of surgery for cardiopulmonary disease, patients who had current severe cardiopulmonary disease, patients with diabetes mellitus, patients with renal dysfunction, and current smokers were excluded from this study. The OLV time within 120 minutes was excluded because it predicted EGL damage was less and if more than 500 mL of bleeding that could lead to transfusion was also exclude. The participants were randomly divided into Group S (sevoflurane anesthesia; n=43) or Group P (propofol anesthesia; n=44) by using a computer-generated randomization table.

Anesthetic management and surgery

All patients fasted since midnight the day of surgery and received intramuscular injection of glycopyrrolate (0.2 mg) before being transferred to the operating room. Upon arrival at the operating room, the patients were attached to electrocardiography, non-invasive blood pressure, and pulse oximetry monitors. Prior to the induction of general anesthesia, a mid-thoracic epidural catheter was placed at T5/6 on all patients for postoperative pain control, and a test dose (3 mL of 2% lidocaine +0.015 mg epinephrine) was injected through the epidural catheter to confirm subarachnoid or intravascular injection. Then, 5 mg/kg thiopental followed by 0.8 mg/kg rocuronium and fentanyl 50–100 μg were intravenously injected to induce anesthesia, after which a double-lumen endobronchial tube (Broncho-Cath; Mallinckrodt Laboratories, Athlone, Ireland) was inserted through the airway. The
position of the endobronchial tube was confirmed using fiberoptic bronchoscopy. A catheter was placed in the radial artery for invasive arterial pressure monitoring, and a central venous catheter was placed in the subclavian vein. The patient was positioned in the lateral decubitus position to reveal the surgical site, which was disinfected before beginning OLV (4–6 mL/kg tidal volume guaranteed pressure ventilation +5 cmH₂O positive end-expiratory pressure). Intraoperative end-tidal CO₂ was maintained at 35–45 mmHg, and peak inspiratory pressure was controlled not to exceed 30 cmH₂O.

After position changed to lateral decubitus position, fentanyl 10 μg/mL in levobupivacaine 0.125% was administered epidurally as a bolus 6 mL, followed by continuous infusion of 2 mL/h.

Group S received 1.5–2.5 vol% sevoflurane, and group P received propofol at 50–150 μg/kg/min to maintain the bispectral index at 40–60. Plasma-lyte (Plasma solution A Inj®; CJ HealthCare, Korea) was used for intraoperative fluid management.

Blood sampling
Blood samples were drawn from all patients immediately after the induction of general anesthesia for baseline measurement (T1). Blood samples were also drawn 60 min after OLV (T2), 120 min after OLV (T3), end of OLV (T4), and after skin suturing (T5). According to previous studies, all blood samples were drawn from patient’s radial artery catheter (10,16).

Heparan sulfate, human syndecan-1, and VCAM1 concentration measurement
Arterial blood samples were drawn into ethylenediaminetetraacetic acid tubes and immediately centrifuged at 1,000 xg for 10 min; the supernatant was then removed and centrifuged for an additional 3 min at 7,000 xg. The plasma was frozen at −80 °C until subsequent analysis. Heparan sulfate, human syndecan-1, and VCAM1 concentrations were analyzed using specific enzyme immunoassay kits (Syndecan-1: Abcam, Cat. No. ab46506, Cambridge, MA, USA; heparan sulfate: Biotang, Cat. No. HU8718, Lexington, MA, USA; VCAM1: Abcam, Cat. No. ab187393, Cambridge, MA, USA). All samples were tested in duplicate. Samples that were over the detection range of the assay were diluted and rerun as needed.

Statistical analysis
All statistical computations were performed using IBM SPSS version 22 (IBM, USA). All variables were presented as mean ± standard deviation. Dichotomous variables such as operation type were compared using Fisher’s exact test. Basal measurement (T1) and measurements at T2–T5 were compared using the repeated measures ANOVA. Group S and Group P were compared at each time point by using the Wilcoxon signed-rank test, and statistical significance was set at a P value <0.05.

Results
Demographic data and procedural characteristics
From among the 87 patients, nine were excluded, specifically for receiving OLV within 120 minutes (n=6), excessive blood loss during surgery (n=2), and re-surgery due to bleeding (n=1) (Figure 1). The patient’s demographic data and procedural characteristics are shown in Table 1. No statistical differences were observed between the two groups in their demographic data. Further, no differences were observed in OLV time, total length of surgery, duration of anesthesia, and fluid volume, which were factors that could affect the outcome.

Surgical techniques and types used for the patients are shown in Table 2. No significant differences were observed between the two groups. All surgeries were performed by two thoracic surgeons.

Heparan sulfate, human syndecan-1, and VCAM1
Changes in heparan sulfate, human syndecan-1, and VCAM1 concentrations across time points are shown in Table 3.

Heparan sulfate concentrations began to increase after beginning OLV and significantly increased from 120 min after OLV (T3) to the end of surgery in both groups (P<0.05). However, there was no statistically significant difference between the both group (P>0.05) (Figure 2). Group P showed a higher heparan sulfate concentration than Group S at all-time points, but without significant intergroup differences (Figure 3).

Human syndecan-1 concentration began to increase about end of OLV (T4) in both groups, and it was significantly elevated at the end of surgery (T5) only in Group S, but there was no statistically significant difference between the both group (P>0.05) (Figure 2). No significant intergroup
differences in human syndecan-1 concentration were observed at any of the time points from T1 to T5 (Figure 3).

VCAM1 concentration did not increase above the basal level in either group (Table 3).

**Discussion**

In this study, lung resection surgery with OLV was temporally correlated EGL damage that was not related to any inflammatory reaction. Compared to propofol, sevoflurane did not show a better protective effect on the EGL.

OLV, which is performed for lung resection surgery is known to be associated with postoperative pulmonary complications and has been reported as a risk factor for ALI (4). The underlying mechanism for OLV-induced ALI involves barotrauma and hyperperfusion/capillary shear stress in the dependent lung and atelectasis-recruitment, ischemia-reperfusion injury, and surgical trauma in the non-dependent lung (5). An injury to the EGL, which forms the inner wall of the alveolar-capillary membrane, plays an important role in such lung injuries (17). Thus, we measured the concentrations of the main components of EGL, namely heparan sulfate and human syndecan-1, in
patients undergoing OLV for lung resection surgery, and compared the concentrations between patients receiving sevoflurane, an inhalational anesthetic, and propofol, an intravenous anesthetic.

In patients undergoing lung resection surgery, the concentrations of heparan sulfate increased with increasing duration of OLV. This is in line with the prevalent knowledge that OLV is a risk factor of lung injury. Further, this supports Licker et al.'s (18) finding that the incidence of ALI increases with increasing area of resection, as it is related to lengthening the duration of OLV.

Heparan sulfate concentration significantly increased from 120 min after beginning OLV in both Group S and Group P, but human syndecan-1 concentration was significantly elevated after skin suturing in Group S. Human syndecan-1 is a core protein strongly bound to the blood vessels, and heparan sulfate is a side chain attached to it. When the EGL is destroyed, the side chain is believed temporally injured before or injured more severely than the core protein attached to the vessels (19).

According to Annecke et al. (15), sevoflurane exerts some protective effects on the EGL against ischemia-reperfusion injury, but in our study, sevoflurane did not significantly decrease the concentrations of EGL damage markers heparan sulfate and human syndecan-1 than did propofol (control). In our experiment, lung resection surgery with OLV was performed for an adequate amount of time (mean duration, 300 min), and the markers were measured at various time points.

Table 3 Changes in heparan sulfate (HS), human syndecan-1 (HS1), and vascular cell adhesion molecule-1 (VCAM1) concentrations across time points

<table>
<thead>
<tr>
<th>Time point</th>
<th>Sevoflurane group (n=38)</th>
<th>Propofol group (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HS (ng/mL)</td>
<td>HS1 (ng/mL)</td>
</tr>
<tr>
<td>T1</td>
<td>9.4±5.4</td>
<td>20.2±9.3</td>
</tr>
<tr>
<td>T2</td>
<td>11.2±6.3</td>
<td>20.2±9.4</td>
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<td>T3</td>
<td>13.3±6.8</td>
<td>20.4±8.9</td>
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<tr>
<td>T4</td>
<td>16.3±8.1</td>
<td>26.4±19.8</td>
</tr>
<tr>
<td>T5</td>
<td>16.1±8.3</td>
<td>28.6±25.6</td>
</tr>
</tbody>
</table>

T1, after the induction of general anesthesia for baseline measurement; T2, blood samples were also drawn 60 min after OLV; T3, 120 min after OLV; T4, end of OLV; T5, after skin suture. OLV, one lung ventilation.

Figure 2 Changes in heparan sulfate (A) and human syndecan-1 (B) concentrations between the groups across time points. There was no significant difference between both groups (repeated measures ANOVA, 95% confidence intervals). T1, after the induction of general anesthesia for baseline measurement; T2, blood samples were also drawn 60 min after OLV; T3, 120 min after OLV; T4, end of OLV; T5, after skin suture. OLV, one lung ventilation.
Figure 3 Comparison of heparan sulfate and human syndecan-1 concentrations between the two groups at each time point. Heparan sulfate and human syndecan-1 concentrations between the sevoflurane and propofol groups are compared at each time point from T1 (baseline measurement) to T5 (after skin suturing). No significant differences are observed in heparan sulfate and human syndecan-1 concentrations between the two groups at any of the time points. The circle is an indicator of the position that is off average.
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Conflicts of Interest: The authors have no conflicts of interest.

In conclusion, lung resection surgery with OLV produced duration-dependent EGL damage that was measured using the concentrations of plasma heparan sulfate and human syndecan-1. Sevoflurane, which is known for its protective effect against ischemia-reperfusion injury, however, did not show any more beneficial effect on EGL than did the intravenous anesthetic propofol.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest.
to declare.

**Ethical Statement:** This study was approved by the hospital's institutional ethics committee (No. PNUYH 05-2014-098), and informed consents were obtained from the patients the day before surgery.

**References**