Effect of Thoracic Epidural Anesthesia with Different Concentrations of Ropivacaine on Arterial Oxygenation during One-lung Ventilation

Yajun Xu, M.D., ‡ Zhiming Tan, M.D., Ph.D., † Shilai Wang, M.D., ‡ Haijun Shao, M.D., ‡ Xuqin Zhu, M.D. ‡

ABSTRACT
Background: Thoracic epidural anesthesia can contribute to facilitate the fast-track approach in lung surgery. However, data regarding the effects of thoracic epidural anesthesia on oxygenation during one-lung ventilation (OLV) are scarce and contradictory. Therefore, the authors conducted a prospective, randomized, double-blinded trial in patients undergoing lung surgery under spectral entropy-guided intravenous anesthesia to evaluate the effects of thoracic epidural anesthesia with different concentrations of ropivacaine on oxygenation, shunt fraction (Qs/Qt) during OLV, and maintenance doses of propofol.

Methods: One hundred twenty patients scheduled for lung surgery were randomly divided into four groups to epidurally receive saline (Group S), 0.25% (Group R0.25), 0.50% (Group R0.50), and 0.75% (Group R0.75) ropivacaine. Ropivacaine was administered intraoperatively (6–8 ml of first bolus + 5 ml/h infusion). Arterial oxygen tension (PaO2) and Qs/Qt were measured before, during, and after OLV.

Results: PaO2 was significantly lower in Group R0.75 compared with that in Group S and Group R0.25 10 min (170 ± 61 vs. 229 ± 68 mmHg, P = 0.01; 170 ± 61 vs. 223 ± 70 mmHg, P = 0.03) and 20 min after OLV (146 ± 52 vs. 199 ± 68 mmHg, P = 0.009; 146 ± 52 vs. 192 ± 67 mmHg, P = 0.03). During OLV, Qs/Qt was significantly higher in Group R0.75 compared with that in Group S and Group R0.25 (P < 0.05); Maintenance doses of propofol were statistically lower in Group R0.75. Vasopressor requirements were higher in Group R0.75.

Conclusion: A decrease in oxygenation during OLV occurred only at the highest dose of epidural local anesthetic and not at lower doses. Higher doses of epidural medication required less propofol and more vasopressors.

What We Already Know about This Topic
- Thoracic epidural analgesia facilitates recovery from lung surgery but may impair oxygenation during one lung ventilation.
- There are no dose response data with epidural ropivacaine in this setting.

What This Article Tells Us That Is New
- In patients with propofol and during one lung ventilation, ropivacaine, 0.75% (6–8 ml bolus, 5 ml/h infusion), resulted in lower PaO2, higher shunt fraction, and greater need for vasopressors than saline or 0.25% or 0.5% ropivacaine.

THORACOTOMY is one of the most painful surgical procedures followed by intense, acute, and chronic pain associated with postthoracotomy.1–3 After thoracotomies, analgesia via an epidural thoracic catheter is an effective and important method of analgesia in the immediate postoperative period.4 The use of thoracic epidural anesthesia (TEA) combined with general anesthesia can contribute to facilitate the fast-track approach for patients undergoing lung surgery.5 So, TEA can be recommended as a standard in lung surgery.6 However, during the operation, TEA with epidural medications may impair oxygenation during one-lung ventilation (OLV), which is an important challenge of thoracic anesthesia.7 As a result of the fact that the pulmonary vasculature is innervated by the autonomic nervous system, hypoxic pulmonary vasoconstriction (HPV) may be influenced by sympathetic neural blockade, thereby altering shunt fraction (Qs/Qt) and arterial oxygenation during OLV. Experimental and clinical studies investigating the effects of TEA on oxygenation showed contradictory results: oxygenation was found to be suppressed,8 unaffected,9–11 or even enhanced.12,13 A recent study14 found that during OLV, TEA did not significantly affect oxygenation and Qs/Qt and can be used safely regardless of whether total intravenous anesthesia (TIVA) or inhalation techniques were used. However, in the study, the authors used a relatively weaker local anesthetic solution (bupivacaine 0.1%) compared with other studies.8–10,12 To our knowledge, there are few data concerning the effects of TEA with different concentrations of local anesthetics on oxygenation and Qs/Qt during OLV.

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Furthermore, in previous studies, concerning the effects of TEA on oxygenation under general anesthesia, maintenance doses of anesthetic agents were made using predetermined doses. This may have led to higher drug administration than was clinically necessary. Spectral entropy, an electroencephalography derivative, has been shown to be a reliable and sensitive monitor of the hypnotic component of anesthesia. Entropy can be an objective help to determine whether and—if so—how much the doses of hypnotics have to be reduced after the local anesthetic administration.

Ropivacaine, a newer local anesthetic, shows many of the properties of other highly liposoluble local anesthetics but benefits from a larger safety margin. The hypothesis of this study was that epidural high concentration ropivacaine impaired arterial oxygenation during OLV. Therefore, we conducted a prospective, randomized trial in patients undergoing lung surgery under spectral entropy-guided intravenous anesthesia in combination with TEA to evaluate the effects of TEA with 0.25, 0.50, and 0.75% ropivacaine on oxygenation, Qs/Qt during OLV, and maintenance doses of propofol.

The primary outcome was to evaluate the effects of different concentrations (0.25, 0.50, and 0.75%) of ropivacaine on arterial oxygenation during OLV. The secondary outcome was to evaluate the effects of epidural ropivacaine on Qs/Qt and maintenance doses of propofol.

Materials and Methods

After approval of the study protocol by the Cancer Hospital, Fudan University Institutional Human Ethics Committee (Shanghai, China), and having obtained written informed consent, 120 American Society of Anesthesiologists physical status I–III patients, aged 21–70 yr, undergoing lung surgery, were included in this prospective randomized, double-blinded, placebo-controlled trial. The study was conducted from October 2008 to April 2009. During the preoperative period, exclusion criteria were general contraindications for epidural anesthesia, impaired arterial oxygenation during OLV, and maintenance doses of propofol.

Anesthetic Technique

All patients received no premedication. Before surgery, an arterial catheter was placed in the radial artery, and a central venous catheter was introduced via the internal right jugular vein into the right atrium, and its position was confirmed by chest radiograph. Standard monitors were applied (GE Datex-Ohmeda S/5, Anesthesia Monitor, Helsinki, Finland). After the skin of the forehead had been carefully wiped with an alcohol swab and then allowed to dry, the Entropy self-adhesive electroencephalogram electrode strips (ZipPrep; Aspect Medical Systems, Newton, MA) were positioned on the forehead, in the four groups of patients. The set of electroencephalogram recording electrodes (Entropy Sensor, Datex-Ohmeda) were applied close to consistent with the manufacturer’s recommendations. State entropy (SE) and response entropy (RE) were calculated by the spectral entropy plug-in module of the same Datex-Ohmeda monitor.

In all patients, an epidural catheter was inserted under sterile conditions through the T7-8 interspace by the paramedian approach using the “loss-of-resistance” technique and was advanced 4-cm cephalad. After an aspiration test for blood and cerebrospinal fluid that yielded negative results, a test dose with 3 ml of lidocaine, 1%, was injected through the catheter by the second anesthesiologist who performed the epidural block. Failure of the test dose to produce sensory or motor anesthesia after 4 min confirmed the absence of an accidental subarachnoid placement of the catheter. In Groups R0.25, R0.50, and R0.75, 6–8 ml of ropivacaine depending on the height and weight of the patient was administered at least 20 min before induction, by the second anesthesiologist, to produce a bilateral segmental sensory block to pinprick between T4 and T12 dermatomes, followed by an infusion of ropivacaine at 5 ml/h using a microinfusion pump, for the duration of surgery. In Group S, 6–8 ml of saline was applied, followed by an infusion of saline at 5 ml/h.

General anesthesia was induced by propofol plasma target-controlled infusion (a target plasma concentration of 4 μg/ml) using Graseby target-controlled infusion pump (Sims Graseby Limited, Waterford, Herts, United Kingdom) and an intravenous injection of midazolam (0.03 mg/kg) and sufentanyl (0.3 μg/kg). Tracheal intubation was facilitated with 0.2 mg/kg cisatracurium when the entropy value reduced to less than 45.

Study Protocol

Patient randomization was established with the use of computer-generated codes. Allocation concealment was established by placing the randomization sequence in consecutively numbered, opaque envelopes. The study was performed by four anesthesiologists in a double-blinded manner as follows: epidural solutions were prepared in a syringe by the first anesthesiologist, who was also responsible for subject grouping. The second anesthesiologist, who was blinded to the type of epidural solutions, performed the epidural block and setting of the epidural infusión. Intraoperative management was performed by the third anesthesiologist, who was blinded to the epidural medication. The variables were recorded by the fourth anesthesiologist, who was blinded to the type of epidural solutions. Patients were randomized into one of four groups to receive epidural saline (Group S), 0.25% (Group R0.25), 0.5% (Group R0.50), and 0.75% (Group R0.75) ropivacaine.

After induction of anesthesia, a double-lumen endobronchial tube (35–39 Ch; Pharmaceutiques RUSCH, Betschdorf, Switzerland) was placed in the patient’s right mainstem bronchus, and endobronchial blockers were inserted into the left mainstem bronchus. OLV was performed from the left side of the thorax to the right side of the thorax. The left mainstem bronchus was occluded with auffed tube. The patients were paralyzed with rocuronium during OLV to maintain muscle relaxation.

Effects of TEA on oxygenation under general anesthesia, maintenance doses of propofol.

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France) was inserted. Left double-lumen tubes were chosen for right thoracotomies, and *vice versa*. The correct position of the tube was determined by auscultation and confirmed by fiberoptic bronchoscopy before and after the patient was in the lateral decubitus position. Ventilatory settings (Fabius Tiro; Dräger, Lübeck, Germany) were identical during two-lung ventilation and OLV: 6 ml/kg tidal volume, a respirator rate to maintain arterial carbon dioxide tension (Paco2) within 35–45 mmHg, inspiratory to expiratory ratio 1:2, and a fraction of inspired oxygen (FiO2) of 1. Positive end-expiratory pressure was not applied. Room temperature was adjusted to 22°C–25°C. Heat loss was prevented by administration of warm intravenous fluids. Esophageal temperature was monitored throughout the operation and maintained at more than 36°C. Anesthesia was maintained with propofol. The doses of propofol were again adjusted to keep the entropy value between 40 and 55. Patients were excluded from the study if two consecutive entropy values were outside the target range (40–55). Cisatracurium was used when the difference between REF and SER (REF – SER) was more than 10 for more than 2 min while entropy level was between 40 and 55. In cases of inadequate analgesia, patients were given additional doses of sufentanil 5–10 μg intravenously.

Inadequate analgesia was defined as response to surgical stimuli by hypertension (systolic blood pressure > 20% above preoperative baseline value for > 5 min), tachycardia (heart rate > 20% above preoperative baseline value), or when the difference between REF and SER (REF – SER) was more than 10 for more than 2 min while entropy level was between 40 and 55. In cases of inadequate analgesia, patients were given additional doses of sufentanil 5–10 μg intravenously.

Fluid administration was limited to 500 ml of hydroxyethyl starch (130/0.4) and 1000 ml of lactated Ringer's solution (500 ml hydroxyethyl starch before epidural insertion and 1000 ml lactated Ringer's solution during surgery). Hypotension and bradycardia were treated with intravenous ephedrine and atropine, respectively. A perioperative antibiotic prophylaxis was given to all patients. Incomplete lung deflation on visual inspection of the surgical field was considered as a criterion for exclusion from the study.

**Study Parameters**

Our experimental protocol consisted of four phases.

1. After induction of general anesthesia during two-lung ventilation with the patient in the lateral decubitus position (T1).
2. During OLV 10 min after collapse of the nondependent lung, in the lateral decubitus position (T2).
3. During OLV 20 min after collapse of the nondependent lung, in the lateral decubitus position (T3).
4. At the end of surgery with two-lung ventilation and the patient in lateral decubitus position (T4).

During each phase, arterial and right atrial blood samples were drawn. The samples were analyzed immediately using a blood gas analyzer (GEM Premier 3000, Lexington, MA), which was calibrated daily according to the manufacture’s instructions. Arterial oxygen tension (Pao2), Paco2, mixed venous oxygenation tension (PvO2), positive airway pressure (Paw), hemoglobin, and the hemodynamic variables (heart rate and mean arterial pressure) were recorded. Entropy values (REF, SER, and REF – SER) were also recorded during each phase. A right atrial blood sample was used to calculate the Qs/Qt instead of the conventional pulmonary arterial blood sample. This method has been used in several studies before.8,14,19,20 Qs/Qt was calculated using the formula:

\[
Qs/Qt = (CcO2 - CaO2)/(CcO2 - CvO2),
\]

whereby

\[
CaO2 = (Pao2 × 0.0031) + (Hemoglobin × 1.36 × SaO2)
\]

\[
CvO2 = (Pvo2 × 0.0031) + (Hemoglobin × 1.36 × SvO2)
\]

\[
CcO2 = ([FiO2 × (Pb - PdO2)] - Paco2)/[Respiratory quotient] × 0.0031) + (Hemoglobin × 1.36)
\]

where \(Pb\) is barometric pressure (760 mmHg); \(PdO2\) 47 mmHg; respiratory quotient, 0.8; \(CcO2\), pulmonary capillary blood oxygen content; \(CaO2\), arterial oxygen content; \(CvO2\), mixed venous oxygen content; \(SaO2\), arterial oxygen saturation; \(SvO2\), central venous oxygen saturation.

All operations were performed by the same surgical team; measurements were done during the time in which the surgeons stopped compressing the operative lung, and the T2 measurements were completed before any pulmonary vessels were ligated. Postoperative analgesia was similar in all groups with patient-controlled epidural analgesia.

Finally, all patients were visited on the first postoperative day and interviewed about intraoperative awareness using the specific Sebel’s score.21

**Statistical Analysis**

All statistical analyses were performed using the SPSS version 12.0 software package (SPSS Inc., Chicago, IL). The primary outcome was to evaluate the effects of different concentrations (0.25, 0.5, and 0.75%) of ropivacaine on oxygenation. The sample size was based on previously published study14 and, with an \(\alpha\) level of 0.05 and a power of 0.8, a minimum of 20 patients per group was needed to detect a difference of 40 mmHg in Paco2 between the groups and a SD of 45 mmHg.

Continuous variables are presented as mean ± SD. The Pearson chi-square test was applied for qualitative variables. Demographic data doses of ephedrine, hemodynamic variables, \(Pao2\), \(Pvo2\), Qs/Qt, and maintenance doses of propofol were compared between the groups using one-way ANOVA followed by a Tukey post hoc test. Two-way repeated-measures ANOVA followed by post hoc multiple comparisons (Tukey test) was used to evaluate the effects of time, group, and interaction. Linear regression was used to analyze the relationship between the dose of ropivacaine (independent variable) and Paco2 as well as Pvo2 (dependent variable) during OLV. All tests were two-tailed, and a \(P\) value < 0.05 was considered statistically significant.
Results

One hundred twenty patients were enrolled in the study. Eleven patients were excluded from the analysis (one in Group S, four in Group R0.25, three in Group R0.50, and three in Group R0.75): five because of difficulties of lung exclusion (one in Group S, two in Group R0.25, one in Group R0.50, and one in Group R0.75), four because of two consecutive entropy values outside fixed limits (two in Group R0.25, one in Group R0.50, and one in Group R0.75), and two because of SpO2 less than 90% (one in Group R0.50 and one in Group R0.75). Statistical analysis was, therefore, conducted with 109 patients: 29 in Group S, 26 in Group R0.25, 27 in Group R0.50, and 27 in Group R0.75 (fig. 1).

The four groups were comparable in terms of age, male:female ratio, weight, height, preoperative arterial blood gas, spirometry results, and the duration of operations (table 1).
Table 2. Blood Gases during Two-lung Ventilation and One-lung Ventilation

<table>
<thead>
<tr>
<th>Variables</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂, mmHg</td>
<td>423 ± 84</td>
<td>229 ± 68</td>
<td>199 ± 68</td>
<td>416 ± 79</td>
</tr>
<tr>
<td>S</td>
<td>426 ± 74</td>
<td>223 ± 70</td>
<td>192 ± 67</td>
<td>409 ± 66</td>
</tr>
<tr>
<td>R₀.₂₅</td>
<td>425 ± 60</td>
<td>206 ± 76</td>
<td>180 ± 59</td>
<td>408 ± 68</td>
</tr>
<tr>
<td>R₀.₅₀</td>
<td>413 ± 68</td>
<td>170 ± 61†</td>
<td>146 ± 52†</td>
<td>404 ± 60</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>39 ± 3</td>
<td>39 ± 5</td>
<td>40 ± 5</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>S</td>
<td>38 ± 4</td>
<td>40 ± 6</td>
<td>39 ± 5</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>R₀.₂₅</td>
<td>39 ± 4</td>
<td>40 ± 5</td>
<td>39 ± 5</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>R₀.₅₀</td>
<td>39 ± 3</td>
<td>39 ± 5</td>
<td>40 ± 5</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 ± 0.04</td>
<td>7.41 ± 0.05</td>
<td>7.40 ± 0.03</td>
<td>7.39 ± 0.03</td>
</tr>
<tr>
<td>S</td>
<td>51 ± 8</td>
<td>50 ± 8</td>
<td>48 ± 7</td>
<td>52 ± 6</td>
</tr>
<tr>
<td>R₀.₂₅</td>
<td>52 ± 10</td>
<td>49 ± 6</td>
<td>46 ± 6</td>
<td>51 ± 8</td>
</tr>
<tr>
<td>R₀.₅₀</td>
<td>51 ± 10</td>
<td>49 ± 8</td>
<td>45 ± 8</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>R₀.₇₅</td>
<td>50 ± 9</td>
<td>48 ± 6</td>
<td>43 ± 5*</td>
<td>51 ± 7</td>
</tr>
<tr>
<td>PVO₂, mmHg</td>
<td>1150</td>
<td>1150</td>
<td>1150</td>
<td>1150</td>
</tr>
<tr>
<td>S</td>
<td>1150</td>
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<tr>
<td>R₀.₂₅</td>
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<tr>
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<td>1150</td>
<td>1150</td>
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<td>1150</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.
* P < 0.05 versus Group S. † P < 0.05 versus Group R₀.₂₅.

PaO₂ = arterial oxygen tension; PaCO₂ = arterial carbon dioxide tension; PVO₂ = mixed venous oxygenation tension; R₀.₂₅ = 0.25% ropivacaine; R₀.₅₀ = 0.5% ropivacaine; R₀.₇₅ = 0.75% ropivacaine; S = saline; T₁ = two-lung ventilation in the lateral decubitus position; T₂ = one-lung ventilation after 10 min; T₃ = one-lung ventilation after 20 min; T₄ = at the end of surgery with two-lung ventilation.

In Group S, ephedrine administration was not required at any time. Twenty-two patients in Group R₀.₂₅, 25 patients in Group R₀.₅₀, and 26 patients in Group R₀.₇₅ required at least one bolus of ephedrine during the study period. The doses of ephedrine in Group R₀.₇₅ was significantly higher than that in Group R₀.₂₅ (18 ± 8 vs. 11 ± 8 mg, P = 0.003; table 1).

Results of blood samples and hemodynamic variables in four measurement times were shown in tables 2 and 3. Two-

Table 3. Data during Two-lung Ventilation and One-lung Ventilation

<table>
<thead>
<tr>
<th>Variables</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>89 ± 11</td>
<td>90 ± 13</td>
<td>88 ± 11</td>
<td>89 ± 12</td>
</tr>
<tr>
<td>S</td>
<td>87 ± 12</td>
<td>86 ± 11</td>
<td>84 ± 15</td>
<td>83 ± 14</td>
</tr>
<tr>
<td>R₀.₂₅</td>
<td>88 ± 16</td>
<td>83 ± 15</td>
<td>80 ± 17</td>
<td>82 ± 16</td>
</tr>
<tr>
<td>R₀.₅₀</td>
<td>84 ± 13</td>
<td>79 ± 17</td>
<td>77 ± 15</td>
<td>76 ± 13</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>77 ± 12</td>
<td>78 ± 15</td>
<td>76 ± 16</td>
<td>79 ± 12</td>
</tr>
<tr>
<td>S</td>
<td>77 ± 13</td>
<td>72 ± 15</td>
<td>74 ± 14</td>
<td>73 ± 14</td>
</tr>
<tr>
<td>R₀.₂₅</td>
<td>73 ± 16</td>
<td>74 ± 16</td>
<td>78 ± 13</td>
<td>75 ± 13</td>
</tr>
<tr>
<td>R₀.₅₀</td>
<td>72 ± 14</td>
<td>73 ± 12</td>
<td>71 ± 16</td>
<td>74 ± 14</td>
</tr>
<tr>
<td>Hb, mg/dl</td>
<td>12.9 ± 1.1</td>
<td>12.8 ± 1</td>
<td>12.6 ± 1.2</td>
<td>12.7 ± 1.2</td>
</tr>
<tr>
<td>S</td>
<td>13.0 ± 0.8</td>
<td>12.8 ± 0.9</td>
<td>12.7 ± 1.3</td>
<td>12.9 ± 1.1</td>
</tr>
<tr>
<td>R₀.₂₅</td>
<td>12.7 ± 0.9</td>
<td>12.5 ± 1</td>
<td>12.6 ± 1.2</td>
<td>12.8 ± 0.9</td>
</tr>
<tr>
<td>R₀.₅₀</td>
<td>13.3 ± 1.0</td>
<td>13 ± 1.1</td>
<td>13.0 ± 0.9</td>
<td>12.8 ± 1.2</td>
</tr>
<tr>
<td>Paw*, cm H₂O</td>
<td>17 ± 3</td>
<td>22 ± 4</td>
<td>22 ± 3</td>
<td>16 ± 3</td>
</tr>
<tr>
<td>S</td>
<td>16 ± 4</td>
<td>22 ± 3</td>
<td>22 ± 4</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>R₀.₂₅</td>
<td>18 ± 3</td>
<td>23 ± 3</td>
<td>22 ± 4</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>R₀.₅₀</td>
<td>17 ± 4</td>
<td>22 ± 4</td>
<td>22 ± 3</td>
<td>18 ± 3</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

Hb = hemoglobin; HR = heart rate; MAP = mean arterial pressure; Paw = positive airway pressure; R₀.₂₅ = 0.25% ropivacaine; R₀.₅₀ = 0.5% ropivacaine; R₀.₇₅ = 0.75% ropivacaine; S = saline; T₁ = two-lung ventilation in the lateral decubitus position; T₂ = one-lung ventilation after 10 min; T₃ = one-lung ventilation after 20 min; T₄ = at the end of surgery with two-lung ventilation.
way ANOVA for $\text{Pao}_2$ showed significant effect of time ($P < 0.0001$) and group ($P = 0.001$; fig. 2). There was no significant interaction of group $\times$ time ($P = 0.58$). During OLV, there was a significant decrease of $\text{Pao}_2$ in four groups of patients ($P < 0.0001$; table 2). Group R0.75 was associated with a lower $\text{PVO}_2$ 20 min after OLV compared with Group S (43 $\pm$ 5 vs. 48 $\pm$ 7 mmHg, $P = 0.045$; table 2). During 20 min after OLV, linear regression analysis showed a significant negative correlation between the dose of ropivacaine and $\text{PVO}_2$. This was described by the regression equation $y = 49 - 1.5x$ ($P = 0.008$; correlation coefficient = $-0.25$) ($y$: $\text{PVO}_2$; $x$: the dose of ropivacaine). No significant differences between the four groups in pH, $\text{PaCO}_2$, airway pressure, heart rate, mean arterial pressure, and hemoglobin were found throughout the study (tables 2 and 3).

$\text{Pao}_2$ was significantly lower in Group R0.75 compared with that in Group S and Group R0.25 10 min (170 $\pm$ 61 vs. 229 $\pm$ 68 mmHg, $P = 0.01$; 170 $\pm$ 61 vs. 223 $\pm$ 70 mmHg, $P = 0.03$) and 20 min after OLV (146 $\pm$ 52 vs. 199 $\pm$ 68 mmHg, $P = 0.009$; 146 $\pm$ 52 vs. 192 $\pm$ 67 mmHg, $P = 0.03$) (fig. 2; table 2). During 10 and 20 min after OLV, linear regression analysis showed a significant negative correlation between the dose of ropivacaine and $\text{Pao}_2$. These were described by the regression equation $y = 255 - 19x$ ($P = 0.001$; correlation coefficient = $-0.30$) and $y = 222 - 17x$ ($P = 0.002$; correlation coefficient = $-0.30$) ($y$: $\text{Pao}_2$; $x$: the dose of ropivacaine), respectively. There was no significant difference between Groups R0.75 and R0.50 in $\text{Pao}_2$.

The calculated Qs/Qt was shown in figure 3. There was a significant increase of Qs/Qt in four groups of patients ($P < 0.0001$; fig. 3). Patients in Group R0.75 had significantly higher Qs/Qt compared with that in Group S and Group R0.25 10 min (39.2 $\pm$ 8.6 vs. 31.6 $\pm$ 8.6, $P = 0.01$; 39.2 $\pm$ 8.6 vs. 32.3 $\pm$ 9.3, $P = 0.03$) and 20 min after OLV (39.9 $\pm$ 7.8 vs. 32.6 $\pm$ 7.7, $P = 0.005$; 39.9 $\pm$ 7.8 vs. 33.8 $\pm$ 8.3, $P = 0.04$).

The propofol plasma target concentration in Groups R0.25, R0.50, and R0.75 was significantly lower than in Group S ($P < 0.0001$; fig. 4) throughout the study. Group R0.75 also had a significantly lower propofol plasma target concentration than Group R0.25 ($P < 0.05$; fig. 4). RE, SE, and RE − SE were similar throughout the studied period in each group (table 4).

All patients were questioned about intraoperative awareness the day after surgery. Every Seb’s score was less than 3, excluding patient awareness. There were no complications associated with the TEA technique (epidural hematoma, neurologic damage, and others).

**Discussion**

The current study demonstrated that problems in oxygenation during OLV only occurred at higher doses of epidural local anesthetic. There was a dose response effect for the different concentrations of ropivacaine. Reasonable concentrations can clearly be used without significant clinical impact. Higher doses of epidural medication required less propofol and more vasopressors.

Previous studies of the effects of TEA on oxygenation during OLV could have been confounded because anesthetic agents were administered at a predetermined dosage. In the...
current study, the administration of anesthetic agents was adjusted to maintain spectral entropy values between 40 and 55. \( \text{RE} - \text{SE} \) is suggested to be a potential surrogate marker of the adequacy of antinociception.\(^{22,23} \) So, in our study, intermittent bolus doses of 5–10 \( \mu \)g of sufentanil intravenously were given if \( \text{RE} - \text{SE} \) was more than 10 for more than 2 min.

The current study demonstrated that propofol requirements were significantly less in the group using high concentration (0.75%) ropivacaine than in the low concentration (0.25%) group. This may result from the difference in intensity of the sensory blockade due to the difference in dosage and concentration of local anesthetics.\(^{24–26} \)

TEA is widely used for intraoperative and postoperative analgesia in thoracic surgical patients. Hypoesthesia should always be considered as an important challenge during OLV. However, there are few studies examining the effects of TEA during OLV on arterial oxygenation and shunt fraction, and the results of these studies are controversial.

In the first clinical study, Garutti et al.\(^8 \) compared TEA + TIVA (propofol + 0.5% bupivacaine) with TIVA (propofol) and discouraged the use of TEA, for the addition of TEA was associated with a significant worsening in oxygenation in OLV because of possible attenuation of HPV. The maintenance dose of propofol was the same in both groups (6–7 mg \( \cdot \) kg\(^{-1} \) \( \cdot \) h\(^{-1} \)) and not adapted to a hypnotic index. In a subsequent study, Von Dossow et al.\(^{12} \) found that TEA (0.50% bupivacaine) in combination with inhalational anesthetics achieved a better oxygenation when compared with TIVA only. This might be attributable to the increase in cardiac output (CO) in the TIVA group after OLV, whereas CO remained stable in the TEA group. But in this study, TEA was not the only different variable between the groups: the choice of general anesthesia (TIVA [without TEA] vs. light inhalational anesthetics [with TEA]) may also have different effects on the results.

Recently, Ozcan et al.\(^{14} \) found that TEA was not associated with a relevant impairment of oxygenation during OLV and can, therefore, be used safely in thoracic anesthesia. But in the study, the authors used a relatively weaker local anesthetic solution (0.1% bupivacaine) compared with other studies.\(^8–10,12 \) Among the long-acting local anesthetics, the S-enantiomer, ropivacaine, is gaining increasing preference for continuous epidural analgesia. So, in our study, we compared the effects of TEA with 0.25, 0.50, and 0.75% ropivacaine on oxygenation, \( Q_s/Q_t \) during OLV.

To eliminate the influence of inhalational anesthetics,\(^{14,27,28} \) we used two anesthesia techniques during OLV: TIVA with or without TEA in the current study. Meanwhile, we inserted the catheter at the thoracic level (T7–T8) to use a smaller volume (estimating 1–1.2 ml for each segment). In addition, the puncture at this level permits analgesia to be limited to T4 and T12 dermatomes.

In our study, there was a lower \( \text{PaO}_2 \) and trend toward a decrease in mean arterial pressure in Group R0.75 because of the cardiovascular effect of TEA. Another possibility may be that in our study fluid loading was deliberately limited to prevent postoperative pulmonary edema. These decreases both suggested that the CO may decrease in the Group R0.75, which was consistent with previous animal study.\(^{13} \) Ishibe et al.\(^{13} \) demonstrated an enhanced HPV response and improved arterial oxygenation during OLV with TEA in dogs, which resulted from decreased CO. The efficacy of HPV is inversely related to CO.\(^{29} \) Significant increase in cardiac indices associated with an increase in pulmonary perfusion can increase \( Q_s/Q_t \).\(^{12,30} \) So, the decrease in oxygenation in Group R0.75 was secondary to the effects of TEA on HPV and probably not on decreased CO.

During OLV, HPV diverts blood flow from the nonventilated lung to the ventilated lung, thereby reducing perfusion of the nonventilated lung, decreasing shunt fraction, and ameliorating the decrease in oxygenation.\(^{31} \) Unfortunately, the anesthetic technique may alter this physiologic response. Because pulmonary vasculature is innervated by the autonomic nervous system, HPV may be influenced by sympathetic neural blockade. Epidural local anesthetics may potentially block sympathetic outflow because the autonomic fibers have a smaller diameter, and they are more easily blocked than sensory or motor fibers.\(^{32} \) Theoretically, a TEA-induced sympathetic block might attenuate the local reflex aspect of HPV. So, spinal mechanism was important to HPV in OLV.

In clinical circumstances, HPV can be affected in two different ways, which can be contrary. First, TEA would enhance the HPV by directing the blood flow to vasodilated areas of the ventilated lung caused by decreased CO\(^{13} \) and by decreasing the general anesthetic requirement. Conversely,
TEA leads to a vasodilation in the nonventilated lung by blocking the thoracic sympathetic system, and therefore, it can attenuate HPV. Furthermore, TEA with different concentrations of local anesthetics may lead to different sympathetic block levels, which may have different effects on HPV, and consequently to different results in oxygenation. This effect may be dose dependent. Although oxygenation between Groups R0.75 and R0.50 during OLV certainly looks like a difference, there was no statistically significant difference. This may be just a loss of power from multiple comparisons. So, in the current study, vasodilation by sympathetic blockade with high concentration (0.75%) ropivacaine counteracts HPV and thereby produces a larger shunt and a decrease in oxygenation during OLV. However, the differences in sympathetic blockade may not explain everything. The one factor may be the likely greater systemic levels of local anesthetic at the higher dose.

Another possibility of the decrease in oxygenation at the highest dose of ropivacaine may be the decrease in P[vO2]. Lower P[vO2] may cause a decrease in oxygenation even with the same shunt fraction. This mechanism may also operate in addition to changes in shunt fraction.

There are several limitations of the current study. First, we did not obtain more invasive data such as CO and pulmonary pressures, which might have better explained the mechanism of our observed oxygenation changes. The placement of pulmonary artery catheters is not a part of our routine practice. Transesophageal Doppler is not appropriate as a characteristic aortic blood flow signal cannot be obtained in half of the patients in the lateral decubitus position.33 Second, one limitation of our study seems to be the use of right atrial blood samples to measure the Qs/Qt instead of pulmonary arterial blood samples. However, there are several studies in which it has been shown that this method can be used to measure the Qs/Qt,20 also in similar studies with OLV.8,14,15 Therefore, results obtained from right atrial blood samples can also be assumed to be reliable. Third, there is no way to completely eliminate confounding factors such as the dose of vasopressor, opioid, and propofol. Because the higher concentrations of local anesthetic in the epidural reduced the amount of propofol used, other factors clearly changed during the study period.

In conclusion, this study demonstrated that the concentrations of epidural local anesthetics sufficient to produce excellent analgesia can be used without clinically significant problems with oxygenation during OLV. Epidural, higher doses of local anesthetic required less propofol and more vasopressors.

References