Thoracic Epidural Analgesia With Levobupivacaine Reduces Remifentanil and Propofol Consumption Evaluated by Closed-Loop Titration Guided by the Bispectral Index: A Double-Blind Placebo-Controlled Study

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**BACKGROUND:** Thoracic epidural analgesia (TEA) combined with general anesthesia decreases anesthetic requirements by half when hemodynamic criteria are used for the titration of analgesia. We therefore determined the impact of TEA on anesthetic requirements, when a closed-loop controller was used allowing the automated coadministration of propofol-remifentanil guided solely by the Bispectral index.

**METHODS:** This single-center double-blind study enrolled patients scheduled for elective posterolateral thoracotomy using TEA. Patients were randomly assigned to receive a bolus followed by a continuous infusion of levobupivacaine 0.5% (levo group) or saline 0.9% solution (saline group). General anesthesia was performed by the same automated controller. Stroke volume optimization guided by an esophageal Doppler probe was performed before randomization. The primary outcome variable was the amount of remifentanil delivered by the automated controller between skin incision and closure. Major arterial hypotension was recorded. Data are presented as medians [interquartile range] or number (%)

**RESULTS:** Nineteen adult patients per group completed the study. At similar depth of anesthesia evaluated by the percentage of time with the Bispectral index in the range 40–60 (85 [77–88] vs 83 [72–87]; P = .39), patients with neuraxial block required less remifentanil (0.15 [0.10–0.20] vs 0.23 [0.14–0.25], µg kg⁻¹ min⁻¹; P = .03) and propofol (4.3 [3.7–4.9] vs 5.7 [4.6–7.3] mg kg⁻¹ h⁻¹; P = .005). Major arterial hypotension was similar in both groups (6 [32%] vs 5 [25%]; P = .46; levo versus saline group, respectively).

**CONCLUSIONS:** Epidurally administered levobupivacaine allowed a decrease by one-third of remifentanil requirement. After stroke volume optimization, major arterial hypotension was similar between groups. (Anesth Analg 2017;125:635–42)

It is common to combine thoracic epidural analgesia (TEA) with general anesthesia (GA) during surgery. Indeed, epidural blockade will partially or completely decrease the nociceptive input originating from the surgical site decreasing the requirement for general anesthetics. Several studies have reported the sparing effect of TEA on intraoperative anesthetic requirements. Sevoflurane concentration was decreased when ropivacaine was epidurally administered to patients undergoing elective surgery. Similarly, propofol requirement for maintenance of anesthesia to achieve Bispectral Index (BIS; Covidien, Dublin, Ireland) between 40 and 50 was reduced by 45% in patients receiving bupivacaine epidurally. Moreover, the maintenance dose of fentanyl was decreased. However, in these previous studies, the fentanyl titration was adjusted according to heart rate or systolic blood pressure changes. In this case, it is a challenge to separate hemodynamic changes related to a deficit of antinoceception or to a sympathetic block related to neuraxial blockade with local anesthetics. Hypotension is common during combined TEA and GA (TEA-GA), and some anesthesiologists are reluctant to administer local anesthetic to avoid hypotension resulting from central sympathetic block, which is a well-known effect of epidural local anesthetic.

An alternative to hemodynamic criteria for opioid administration during GA is titration using electroencephalogram activity (EEG). Indeed, the EEG has previously been used for the determination of remifentanil pharmacodynamics. A controlled trial reported that the BIS change was as sensitive as hemodynamic responses after painful stimuli. We have developed a controller allowing the automated titration of propofol and remifentanil guided by the BIS. The dual-loop controller is based on a proportional-integrative-derivative algorithm that maintains the BIS value automatically in the range 40 to 60. An automated controller of drug delivery is a robust, reproducible, and unbiased method for the assessment of anesthetic requirement in...
obese patients,\textsuperscript{10} in pediatric patients,\textsuperscript{11} during orthotopic liver transplantation,\textsuperscript{12} or when an adjunct was used such as nitrous oxide\textsuperscript{13} and dexmedetomidine,\textsuperscript{14} or when different propofol formulations were evaluated\textsuperscript{15} because investigator bias is eliminated.

The objective of the current study was to determine specifically the sparing effect of TEA on remifentanil in adult patients undergoing elective posterolateral thoracotomy between skin incision and closure. This study tested 1 local anesthetic levobupivacaine with 1 concentration (0.5\%) administered epidurally without opioid or \(\alpha\)-agonist. We tested the hypothesis that neurexial block decreases the amount of remifentanil given by the dual-loop controller to maintain a similar depth of anesthesia measured by the BIS during the surgical procedure. The secondary outcomes were the amount of propofol delivered by the automated controller and the incidence of major arterial hypotension recorded after stroke volume optimization.

**METHODS**

This randomized, double-blind, placebo-controlled clinical trial was approved by an Institutional Ethics Committee (Comité de Protection des Personnes dans la Recherche Biomédicale, Hôpital A. Paré, N°081282, Boulogne Billancourt, France) and the relevant French regulatory office (Agence Française de Sécurité Sanitaire des Produits de Santé), and registered on ClinicalTrials.gov (NCT00627081). Information and written consent were provided during the investigator’s visit the day before the surgery. All patients were enrolled at the private university hospital of Hôpital Foch (Suresnes, France).

**Patients**

Consecutive patients scheduled for a posterolateral thoracotomy for a lung resection and treated by one of the authors (V.D.-N.) between February 2008 and December 2010 were included if they were older than 18 years with an American Society of Anesthesiologists status score from I to III. Exclusion criteria were pregnancy, patients with a central neurological disorder, a pacemaker, cerebral lesion, psychotropic treatment, anticonvulsant treatment, preoperative analgesic treatment with opioids, allergy to propofol, to remifentanil, or to a muscle relaxant, and contraindication of TEA (such as hypersensitivity reaction to local anesthetic, coagulation disorders, and systemic or local infection). Moreover, patients undergoing elective pneumonectomy, patients with failure of epidural placement (patients with the presence of blood in the epidural catheter were considered to be patients with a failed epidural analgesia) or with an incomplete datasheet, were excluded from the study.

Patients were randomly assigned by an Internet-based randomization system in a 1:1 ratio into the saline 0.9\% (saline group) or levobupivacaine groups (levo group) after stroke volume optimization. Patients and care providers were blinded to randomization. Syringes of levobupivacaine 0.5\% (Chirocaine 5 mg·mL\(^{-1}\); Abbott, Rungis, France) and of saline were prepared by a physician not involved in the study; the drug and placebo were colorless and indistinguishable. In the saline group, the epidural was infused with a first bolus of saline followed by a continuous infusion of saline at 5 mL·h\(^{-1}\). Ten minutes before the end of surgery, patients received a bolus of levobupivacaine 0.5\% in the epidural space with 20 \(\mu\)g sufentanil. In the levo group, the epidural was first infused with a bolus of levobupivacaine 0.5\%, followed by a continuous infusion of levobupivacaine 0.5\% at a rate of 5 mL·h\(^{-1}\). In the levo group 10 minutes before the end of the surgery, patients received a bolus of saline serum with 20 \(\mu\)g sufentanil in the epidural space. The volume of the initial bolus or the bolus administered before the end of the surgery was determined according to the patient’s height (6 mL if the height is <170 cm and 8 mL above) and was administered in supine position after checking the absence of blood reflux in the epidural catheter. Surgical incision was allowed 15 minutes after the initial bolus.

**Procedure**

One hour before surgery, patients received a premedication of 1 g paracetamol and 1 mg·kg\(^{-1}\) hydroxyzine orally. Upon arrival in the operation room, patients were monitored as usual with an electrocardiogram, arterial oximetry, noninvasive blood pressure followed by invasive blood pressure after the induction, core temperature, and neuromuscular monitoring using the AS/5 monitor (GE Healthcare, Helsinki, Finland) and BIS monitor (A 2000 XP version 3.11) with a forehead probe. A dedicated intravenous cannula including a 3-way adaptor was placed, allowing an independent way for fluid (250 mL Ringer’s solution was infused during the induction followed by an infusion rate of 2 mL·kg\(^{-1}\)·h\(^{-1}\)), propofol, and remifentanil administration. An epidural catheter was inserted in sitting position through a 17-gauge Tuohy needle at T5-T6 or T6-T7 level. A test dose of 5 mL lidocaine 2\% with 5 \(\mu\)g·mL\(^{-1}\) epinephrine was administered to rule out an intravascular or intrathecal location of the catheter. Five minutes later, the TEA was tested with hot-cold stimulus. This test was performed again at the arrival in the recovery room, and patients were excluded if the test was negative.

For all patients, GA was provided by the automated titration of propofol and remifentanil guided by the BIS during the whole anesthetic period including induction using the same closed-loop controller in both groups. The controller used in this study has the same gain constants, which were previously validated in a randomized controlled study.\textsuperscript{9} The controller was described in detail in this study. The controller modifies the propofol\textsuperscript{16} or remifentanil\textsuperscript{17} effect site concentrations automatically according to BIS changes. The dual closed-loop assumption is that small fluctuations of BIS are related to intensity of nociception and are a surrogate measure of the deficit of antinociception. The small variation of BIS modifies only the remifentanil; but when the variation is large, both remifentanil and propofol are modified. Atracurium was administered to facilitate tracheal intubation and was monitored at the adductor pollicis using Neuromuscular Transmission (GE Healthcare), a left-sided double-lumen tube was inserted and controlled by a fiberoptic bronchoscope. Patients were kept normothermic using a forced-air warming blanket associated with a fluid warming device. A radial artery catheter on the opposite wrist to the surgery and an esophageal Doppler probe (Deltex Medical, Chichester, UK) were inserted after...
Epidural analgesia was oriented in the recovery room. Recall of intraoperative sensations was assessed through a pinprick test to assess the level of analgesia was determined between skin incision and the end of wound closure. Hemodynamic data were reported every 5 minutes.

Vasopressor and surgical timing (lateral positioning, incision, one-lung ventilation, and skin closure) were collected. Vasopressor administration and were major when phenylephrine and/or norepinephrine were administered. At each episode of BIS$_{>60}$ we determined whether BIS$_{>60}$ was associated with an increase of heart rate or mean arterial pressure greater than 20%.

**Statistical Analyses**

Continuous variables were described as median and interquartile range [IQR] and compared using the Mann-Whitney U test. Categorical variables, expressed as numbers and frequencies or frequencies with 95% confidence interval (CI), were calculated using the Wilson procedure with a correction for continuity and were compared by the Fisher exact test. Probability values less than .05 were considered statistically significant. Data analysis was performed using SPSS version 11.0 (SPSS Science, Inc, Chicago, IL).

Primary outcome was the amount of remifentanil delivered by the closed-loop system. The sparing effect of TEA on opioid consumption varied between 42% and 88%. In a pilot study that we performed, the mean ± SD consumption of remifentanil during a posterolateral thoracotomy without epidural analgesia was above 0.21 ± 0.06 µg·kg$^{-1}$·min$^{-1}$. We expected a decrease of drug consumption of 30% (0.21 vs 0.14 µg·kg$^{-1}$·min$^{-1}$), considering this value as clinically relevant related to the adverse events to TEA. We therefore calculated that a total of 32 patients (16 per group) had to be recruited to demonstrate such a difference with a 90% power for a 2-sided α-error of 0.05 and common standard deviation of 0.06 µg·kg$^{-1}$·min$^{-1}$ (epiR package 0.9-30, R Foundation for Statistical Computing, Vienna, Austria). We planned to recruit 40 patients under the assumption that some would be excluded for various reasons.

**RESULTS**

Among 45 eligible patients, 40 patients were finally enrolled and randomized into 2 groups. And finally 19 patients per group had completed data (Figure 1). Epidural analgesia appeared efficacious in all cases. Demographic and treatment characteristics are presented in Table 1.

At a similar depth of anesthesia during the surgical procedure, remifentanil consumption was decreased (0.15 [0.10–0.20] vs 0.23 [0.14–0.25] µg·kg$^{-1}$·min$^{-1}$; $P = .03$) by 35% (95% CI, 16-60) but also the number of target modifications of remifentanil decided by the controller (Table 2) in the levo group compared with the saline group. Moreover, propofol consumption was decreased by 25% (95% CI, 10-49) in the levo group, while induction was achieved with similar

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**Figure 1.** Trial profile.
TEA and IV Anesthesia

criteria modified the relationship between a light anesthesia episode and hemodynamic variables. We found a poor relationship between BIS values and stroke volume increases in patients with light anesthesia episodes, with BIS values between 40 and 60 (BIS<60), and deep anesthesia or BIS value >60 (BIS>60) were similar between the 2 groups as presented in Table 2. The number of light anesthesia episodes per patient is presented in Table 2. We found a poor relationship between a light anesthesia episode and hemodynamic criteria modifications. In the 2 groups, a total of 32 episodes of BIS<60 were recorded and 44% (95% CI, 27-62) of BIS<60 were associated with a significant increase in heart rate or mean arterial pressure.

Stroke volume optimization increased stroke volume in 84% of patients in saline group (16/19) and in 100% of patients (19/19) in the levo group with P = .59. The median increases in stroke volumes were 31% (95% CI, 13-56) in saline group and 24% (95% CI, 9-49) in levo group (Table 3). The total amounts of preoperative colloid to obtain stroke volume optimization were similar between the 2 groups. Intraoperative fluid and vasoactive drug management were similar in both groups during anesthesia. Five patients in the saline group required phenylephrine to restore initial systolic arterial pressure versus 6 in the levo group (P = .46; Table 3). All TEA catheters were tested in the recovery room and appeared correctly placed and symmetric.

No cases of awareness with recall were reported.

**DISCUSSION**

The current study demonstrates that TEA with levobupivacaine during posterolateral thoracotomy reduces by one-third the remifentanil consumptions automatically administered by a closed-loop controller guided by the electrocortical activity. TEA also decreases propofol consumption, and the hemodynamic impact of sympathetic block was limited after stroke volume optimization.

In the current study, the automated controller continuously maintained the BIS value in the range 40 to 60 in both groups. An EEG activation related to a deficit of antinociception increases the BIS value, and the controller increases remifentanil concentrations to maintain the BIS in the range. In particular for the levo group, the nociceptive output originating from the surgical site was partially blocked by the TEA and EEG activation episodes decrease. Because the BIS value is lower, the controller will decrease the remifentanil concentration to avoid drug overdosing and also the number of decisions of target modification (Table 2). This trial is a proof of concept that the anesthetic drug requirement determined by an automated controller using the BIS is a method to determine the impact of TEA in remifentanil consumption. In previous studies, the titration of different drugs was left to the practitioner’s decision using clinical hemodynamic criteria. Indeed, hemodynamic changes during combined TEA-GA are poor indicators of the deficit of antinociception during thoracotomy. Hemodynamic changes are influenced by the sympathetic block related to TEA; by the patient such as preoad, chronic hypertension, heart failure, or acute arrhythmia; by the surgery such as manipulation of great vessels or blood loss; and by the intraoperative treatment such as fluid administration or vasopressor use. For the fentanyl consumption during maintenance of GA, the sparing effect reported for combined TEA-GA was from 40% to 88% in patients scheduled for elective thoracic surgery when the titration of fentanyl was performed depending on hemodynamic

### Table 1. Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Saline Group (n = 19)</th>
<th>Levo Group (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>64 [55–74]</td>
<td>55 [49–67]</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>10 (50%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>168 [160–173]</td>
<td>173 [163–182]</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>71 [52–80]</td>
<td>68 [58–81]</td>
</tr>
<tr>
<td><strong>ASA I–II/III</strong></td>
<td>17 (85%/3 (15%)</td>
<td>17 (89%/2 (11%)</td>
</tr>
<tr>
<td><strong>Preoperative cardiovascular</strong></td>
<td>12 (60%)</td>
<td>13 (68%)</td>
</tr>
<tr>
<td><strong>treatment</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as median [IQR] or number (%).

**Abbreviations:** ASA, American Society of Anesthesiologist’s physical status score; levo group, patients receiving epidural infusion of levobupivacaine; preoperative cardiovascular treatment, β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or diuretics; saline group, patients receiving epidural infusion of isotonic saline.

### Table 2. Drug Consumptions and Performance of the Controller During Maintenance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Saline Group (n = 19)</th>
<th>Levo Group (n = 19)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration (min)</strong></td>
<td>152 [140–205]</td>
<td>160 [142–178]</td>
<td>.99</td>
</tr>
<tr>
<td><strong>Remifentanil</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose (μg·kg⁻¹·min⁻¹)</td>
<td>0.23 [0.14–0.25]</td>
<td>0.15 [0.10–0.20]</td>
<td>.03</td>
</tr>
<tr>
<td>Number of target modifications</td>
<td>45 [40–51]</td>
<td>37 [31–40]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Propofol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose (mg·kg⁻¹·h⁻¹)</td>
<td>5.7 [4.6–7.3]</td>
<td>4.3 [3.7–4.9]</td>
<td>.005</td>
</tr>
<tr>
<td><strong>BIS values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIS&lt;40</td>
<td>83 [72–87]</td>
<td>85 [77–88]</td>
<td>.39</td>
</tr>
<tr>
<td>BIS&lt;60</td>
<td>12 [6–22]</td>
<td>9 [7–17]</td>
<td>.01</td>
</tr>
<tr>
<td><strong>SR</strong></td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are median [IQR].

**Abbreviations:** BIS<40, percentage of time during which the BIS value was between 40 and 60 during maintenance; BIS>60, percentage of time during which the BIS value was less than a value of 40; BIS<60, percentage of time during which the BIS value was greater than a value of 60; levo group, patients receiving epidural infusion of levobupivacaine; saline group, patients receiving epidural infusion of isotonic saline; SR, burst suppression ratio incidence (ie, patients who presented a suppression ratio >10% during more than 1 minute).
criteria. In the current study, the remifentanil titration was performed automatically without the use of clinical and hemodynamic criteria. Finally, an automated controller is an objective, reproducible method to determine the impact of combined TEA-GA in anesthetic consumptions because investigator bias is eliminated.

**Figure 2.** Bispectral index (BIS) values and calculated effect-site concentration (Ce) of propofol and remifentanil. Individual values are shown; data are averaged for graphical representation with a moving average filter of 1-minute duration. Median values (thick line) are presented with 10th and 90th percentiles (thin line). Levo indicates patients receiving epidural infusion of levobupivacaine; saline, patients receiving epidural infusion of isotonic saline.

**Figure 3.** Histogram of remifentanil and propofol consumptions. Gray histograms represent the levo group = patients receiving epidural infusion of levobupivacaine and white histograms represent the saline group = patients receiving epidural infusion of isotonic saline. Normal distribution curve for levo group (solid line) and saline group (dashed line).
The sparing effect of combined TEA-GA was 50% for sevoflurane when the titration was assessed by the movement of the patient after tetanic electrical stimulation.\(^1\) The sparing effect decreased to 34% when the titration was assessed using a target BIS value.\(^1^9\) Bupivacaine administered epidurally before induction of GA allowed a decrease of propofol requirement by 45% to 62% during induction and 45% to 58% during maintenance of GA when the propofol titration was guided by the BIS.\(^4,20\) The sparing effect in previous studies was higher than in our study, but no data were given about the depth of anesthesia measured by the BIS and probably the investigators were influenced by hemodynamic criteria, whereas in the current study the drug titration was performed independently of clinical and hemodynamic criteria.

Moreover, no studies have reported stroke volume optimization to decrease the hemodynamic instability related to variability of patient preload. The sympathetic blockade decreases preload, cardiac output, and hepatic blood flow, which modifies the propofol clearance. A pharmacokinetic study demonstrated that lumbar epidural blockade with ropivacaine decreases the propofol clearance by 30% related to the hemodynamic alteration.\(^25\) In the current study, all patients in both groups received colloid, and preload optimization increased the stroke volume in 92% (35/38) of patients (Table 3) and can explain the difference between the current and the previous studies.

Syrnpathetic block related to TEA can promote arterial hypotension, potentially worsened by hypnotic drugs.\(^22\) Consequently, epidural analgesia has been recommended with a lower concentration of local anesthetic and lower volumes to markedly reduce the impact of this sympathetic block.\(^3\) Nevertheless, the occurrence of major arterial hypotension was similar to the control group, and this result was unexpected.\(^6,23\) The decrease of major hypotension was emphasized by stroke volume optimization before epidurally administered levobupivacaine. Major arterial hypotension of combined TEA-GA (Table 3) was low compared with the Perioperative Ischemic Evaluation 2 (POISE-2) trial, which reported in 564 patients an incidence of clinically important hypotension of 70%.\(^24\) Studies have reported hypotension related to sympathetic block, but no studies have reported hypotension associated with a surrogate measure of preload or the sympathetic tone. In our study, preoperative fluid optimization (Table 3) could be considered as high even though no in-hospital complications were reported. Nevertheless, care should be taken regarding fluid management especially in lung surgery where overfilling (fluid intake more than 9 mL·kg\(^{-1}\)·h\(^{-1}\)) has been shown to increase morbidity and mortality,\(^25\) but the use of goal-directed fluid therapy in thoracic surgery limits the risk of fluid overfilling.\(^26\) Moreover, continuous automated titration of propofol and remifentanil leads to reduction of anesthetic requirements, avoiding drug overdosing and consequently may prevent any related arterial hypotension events.\(^9\) Moreover, the use of an automated controller improves the mean arterial pressure of surgical patients.\(^27\)

### Limitations of the Study

A test dose of lidocaine with epinephrine was administered in the saline group and lidocaine might produce significant analgesia. However, lidocaine was administered in both groups, and anesthetic consumptions were different (Table 2). Probably in the absence of lidocaine in saline group, the difference of anesthetic consumptions will be larger. Systemic local anesthetic administration has anesthetic properties;\(^1\) in particular, lidocaine can modify depth of anesthesia measured by the BIS.\(^29\) In the current study, no intravenous levobupivacaine was administered in the saline group because intravenous levobupivacaine has cardiovascular toxicity\(^29\) and the sparing effect of TEA can be overestimated. The study could underestimate the sparing effect of anesthetics because thoracotomy was performed in lateral decubitus position and local anesthetic was administered in supine position that could lead to a partial lateralization of the analgesic effect related to a short delay from injection to patient positioning. However, postoperative pain assessment did not find asymmetry, and the influence of the position for the spread of local anesthetic has no clinical significance during epidural anesthesia.\(^30\) Another limitation comes from a potential decrease in cardiac output in the levobupivacaine group that could modify hepatic blood flow and finally the clearance of propofol.\(^31\) Moreover, the

### Table 3. Fluid and Vasoactive Drugs Management

<table>
<thead>
<tr>
<th></th>
<th>Saline Group ((n = 19))</th>
<th>Levo Group ((n = 19))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Postinduction stroke volume optimization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV before optimization (mL)</td>
<td>69 [51–94]</td>
<td>73 [66–99]</td>
<td>.27</td>
</tr>
<tr>
<td>SV after optimization (mL)</td>
<td>114 [77–127]</td>
<td>105 [87–115]</td>
<td>.88</td>
</tr>
<tr>
<td>SV %</td>
<td>31 [13–54]</td>
<td>24 [8–56]</td>
<td>.26</td>
</tr>
<tr>
<td>Fluid challenge with colloid (mL·kg(^{-1}))</td>
<td>10 [7–17]</td>
<td>12 [7–14]</td>
<td>.57</td>
</tr>
<tr>
<td><strong>Intraoperative fluid management</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ringer lactate (mL)</td>
<td>1117 [875–1500]</td>
<td>1017 [1000–1000]</td>
<td>.58</td>
</tr>
<tr>
<td>Colloid (mL)</td>
<td>971 [500–1125]</td>
<td>866 [500–1375]</td>
<td>.56</td>
</tr>
<tr>
<td><strong>Undesirable hemodynamic effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor—epinephrine</td>
<td>15 (75)</td>
<td>13 (68)</td>
<td>.73</td>
</tr>
<tr>
<td>Major—phenylephrine or norepinephrine</td>
<td>5 (25)</td>
<td>6 (32)</td>
<td>.46</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>1</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are median [IQR] or number (%).

Abbreviations: levo group, patients receiving epidural infusion of levobupivacaine; saline group, patients receiving epidural infusion of isotonic saline; severe bleeding, blood loss >500 mL; SV, stroke volume; SVV, stroke volume variation.
same relationship was found between cardiac output and remifentanil plasma concentrations. Nevertheless, stroke volume optimization could have decreased this event. The results of this study were related to one levobupivacaine concentration administered, and certainly by adding opioids, α2-agonist, or the use of another local anesthetic (bupivacaine or ropivacaine), the results would be different. We did not evaluate the clinical impact of combined TEA-GA in the postoperative period such as the length of stay in the recovery room or cognitive recovery, and this study was not powered to demonstrate this.

CONCLUSIONS
During combined TEA-GA with levobupivacaine, the nociceptive input originating from the thoracotomy is partially blocked at the spinal level. Using an unbiased method, we reported a reduction by one-third of remifentanil but also one-quarter of propofol requirements. The intraoperative hemodynamic impact of TEA can be limited after preload optimization.

DISCLOSURES
Name: Virginie Dumans-Nizard, MD.
Contribution: This author helped conduct the study and write the manuscript.

Conflicts of Interest: None.

Name: Morgan Le Guen, MD, PhD.
Contribution: This author helped design the study and write the manuscript.

Conflicts of Interest: None.

Name: Edouard Sage, MD, PhD.
Contribution: This author helped conduct the study and write the manuscript.

Conflicts of Interest: None.

Name: Thierry Chazot, MD.
Contribution: This author helped design the study, perform data analysis, and write the manuscript.

Conflicts of Interest: Thierry Chazot is a cofounder of MedSteer, which is a biomedical society to promote research and development of closed-loop tools.

Name: Marc Fischler, MD.
Contribution: This author helped design the study and write the manuscript.

Conflicts of Interest: Marc Fischler is the president of the Scientific Committee of MedSteer, which is a biomedical society to promote research and development of closed-loop tools.

Name: Ngai Liu, MD, PhD.
Contribution: This author helped design the study, perform data analysis, and write the manuscript.

Conflicts of Interest: Ngai Liu is a cofounder of MedSteer, which is a biomedical society to promote research and development of closed-loop tools.

This manuscript was handled by: Richard Brull, MD, FRCPC.

REFERENCES