Article
Assessment of Total Ropivacaine Concentration in Blood after Bilateral Pecto-Intercostal Fascial Block Combined with Rectus Sheath Block in Cardiac Surgery Patients

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Abstract

Objectives: Pecto-intercostal fascial block (PIFB) and rectus sheath block (RSB) have been combined to offer better analgesia for cardiac surgery patients, but safety of the analgesic protocol with a large volume of ropivacaine is uncertain. Methods: This is a prospective observational study at Peking University People’s Hospital to investigate the pharmacokinetic profile of ropivacaine after combined regional blocks. Patients undergoing elective cardiac surgery by a median sternotomy were enrolled to receive bilateral PIFB and RSB with 70 mL 0.3% ropivacaine (total dose 210 mg). Blood was sampled at 5, 10, 15, 30, 60, 90 and 120 mins after blocks. Total blood concentration of ropivacaine for patients were measured. Results: Ten patients were enrolled and analyzed. The peak total ropivacaine concentration varied from 0.67 to 2.42 µg/mL. Time to reach the peak values mainly located between 10 and 30 mins after the performance. No patients had ropivacaine concentration values above toxic threshold (4.3 µg/mL), and there were no systemic toxicity symptoms during the perioperative period. Conclusions: PIFB combined with RSB in a general injection of 70 mL 0.3% ropivacaine does not give rise to toxic levels, and it is an effective and safe analgesic protocol for cardiac surgery patients.

Keywords
pecto-intercostal fascial block; ropivacaine; rectus sheath block; cardiac

Introduction
Pain after cardiac procedures is catastrophic and persistent, and many patients endure more pain postoperatively than they expect to preoperatively [1]. Adequate analgesia is essential to enhance recovery. In recent years, fascial plane blocks have become available in cardiac surgery as part of multimodal analgesia. Considering the multidimensional pain in cardiac surgery, pecto-intercostal fascial block (PIFB) and rectus sheath block (RSB) have been combined to cover the pain generated from incision of sternotomy and subxiphoid chest tube [2,3].

The potency, concentration and volume of local anesthetics used in regional techniques have been discussed to achieve a balance between efficacy and safety. For fascial plane blocks, known as “volume blocks”, analgesia depends on the sufficient spread of local anesthesia with adequate volume [4]. The larger the volume of a single injection, the wider the contact area with adjacent tissues, and the more local anesthetics would be absorbed into the blood. The product of concentration and volume is the real dose for a single fascial plane injection of local anesthetics. The maximum allowed milligram dose of local anesthetics may vary for patients with cardiovascular diseases compared to healthy volunteers, as changing cardiomyocyte intracellular calcium dynamics would mediate local anesthetic cardiac toxicity [5]. Besides, the absorption of local anesthetics may be attenuated due to insufficient tissue perfusion resulting from decreased cardiac function. The changes in the plasma concentrations of local anesthetics with larger volumes after a single injection into the fascial planes for patients undergoing cardiac surgery are still uncertain.

This observational study is intended to estimate peak total ropivacaine concentrations in plasma after ultrasound-guided PIFB combined with RSB by a relatively high volume of ropivacaine (70 mL, 0.3%) and evaluate the safety of this analgesic pattern for cardiac patients.

Methods and Materials

Patients
This research was approved by Ethical Review Committee of Peking University People’s Hospital (#2022PHB179-001). Patients aged 18 to 75 years who...
were judged as American Society of Anesthesiologists II–III and scheduled for PIFB and RSB before elective cardiac surgery by a median sternotomy were included. Patients with known allergy to ropivacaine, coagulation disorders, infections at puncture sites, opioid abuse and cognitive dysfunction were excluded. Written informed consent was obtained from all the patients.

**Anesthesia and Analgesia**

All patients were continuously monitored by noninvasive arterial blood pressure, five-lead electrocardiography (ECG), pulse oxymoglobin saturation, invasive arterial blood pressure, temperature, urine output and bispectral index (BIS). Anesthesia induction was performed with 0.02–0.04 mg/kg midazolam, 0.2–0.4 mg/kg etomidate, 1–1.5 µg/kg sufentanil and 0.2–0.3 mg/kg cisatracurium. Anesthesia maintenance was performed with propofol, sevoflurane, dexmedetomidine and cisatracurium to guarantee the BIS of approximately 45–55. Bolus sufentanil (0.3–0.5 µg/kg) and vasoactive drugs were given by supervising anesthesiologists. After surgery, patients were transferred to the intensive care unit (ICU) for extubation and further medical care. All patients received patient-controlled intravenous analgesia (PCIA) with a standard regimen of hydro-morphine (no basal infusion, 0.2 mg bolus and 10-minute lockout intervals). Postoperative pain was assessed using a 10-point numeric rating scale (NRS) at rest or deep breath at 12, 24 and 48 hours after surgery.

**Combined Regional Block Performances**

Bilateral PIFB was performed at supine position under ultrasound guidance after anesthesia induction. The high-frequency linear ultrasound probe (EPIQ7C, PHILIPS, Amsterdam, The Netherlands) was placed 2–3 cm at the fourth intercostal space next to the sternum. A 21-gauge needle (SonoPlex STIM, PAJUNK, Geisingen, Germany) was inserted into the plane between the pectoralis major muscle and intercostal muscle using an in-plane technique. After verification by visualizing the muscle separation upon injection of saline, 20 mL 0.3% ropivacaine containing 2.5 mg dexamethasone was delivered to each side.

Bilateral RSB was performed after PIFB with the same position and probe. The probe was placed next to the xiphoid in the epigastric region. The needle was inserted into the plane between the rectus abdominal muscle and its posterior sheath. After verification by visualizing the structure separation upon injection of saline, 15 mL 0.3% ropivacaine containing 2.5 mg dexamethasone was delivered to each side.

**Blood Samples**

Blood samples were obtained at 5, 10, 15, 30, 60, 90 and 120 mins after PIFB and RSB procedures from the radial arterial cannula. Subsequent blood samples were waived when cardiopulmonary bypass started. Plasma samples were reserved frozen at –80 °C for 2–4 months prior to analysis. An ultra-high performance liquid chromatography-tandem triple quadrupole mass spectrometry method was established to determine total ropivacaine concentrations in plasma at different timepoints. The definite and validation characteristics of this method have been introduced [6].

**Statistics**

All statistical analyses were performed using GraphPad Prism 9.0 software (GraphPad Prism, San Diego, CA, USA) for Windows. The results are presented as mean (standard deviation).

**Results**

Ten patients were enrolled and analyzed. Demographic characteristics, peak total arterial ropivacaine concentration (Cmax) and time to reach Cmax (Tmax) are shown in Table 1. The specific ropivacaine concentration at different timepoints for all patients are shown in Fig. 1. The peak total ropivacaine concentration varied from 0.67
Table 1. Demography characteristics and peak ropivacaine concentration (µg/mL).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>EF before surgery</th>
<th>ASA</th>
<th>Surgery</th>
<th>CPB</th>
<th>Surgical time (min)</th>
<th>Anesthetic time (min)</th>
<th>Ropivacaine Dose (mg/kg)</th>
<th>Cmax (µg/mL)</th>
<th>Tmax (min)</th>
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<td>76</td>
<td>65</td>
<td>III</td>
<td>CABG</td>
<td>No</td>
<td>319</td>
<td>405</td>
<td>2.8</td>
<td>1.31</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>Male</td>
<td>68</td>
<td>65</td>
<td>III</td>
<td>AVR</td>
<td>Yes</td>
<td>400</td>
<td>497</td>
<td>3.1</td>
<td>1.90</td>
<td>30</td>
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<td>3</td>
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<td>Female</td>
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<td>63</td>
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<tr>
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<td>Female</td>
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<td>67</td>
<td>III</td>
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<td>327</td>
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<td>2.36</td>
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<tr>
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<td>75</td>
<td>63</td>
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<td>0.97</td>
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<td>58</td>
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<td>394</td>
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<td>372</td>
<td>3.4</td>
<td>2.42</td>
<td>30</td>
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</table>

ASA, American Society of Anesthesiologists; AVR, aortic valve replacement; CABG, cardiac artery bypass graft; CPB, cardiopulmonary bypass; EF, ejection fraction; MVR, mitral valve replacement.

Table 2. Postoperative NRS and clinical outcomes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>NRS (R/D) at 12 h</th>
<th>NRS (R/D) at 24 h</th>
<th>NRS (R/D) at 48 h</th>
<th>Hydromorphone consumption within 24 h (mg)</th>
<th>Hydromorphone consumption within 48 h (mg)</th>
<th>Pain at the chest tube within 48 h</th>
<th>Time to extubation (h)</th>
<th>LOS in ICU (h)</th>
<th>Time to chest tube removal (h)</th>
<th>LOS in hospital (d)</th>
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<td>0/1</td>
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<td>5.4</td>
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<td>4.0</td>
<td>21.0</td>
<td>70.0</td>
<td>13</td>
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<td>1/2</td>
<td>0/2</td>
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<td>5.0</td>
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<td>2/2</td>
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<td>44.5</td>
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<td>0/1</td>
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<td>0/1</td>
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<td>7.0</td>
<td>46.4</td>
<td>71.7</td>
<td>11</td>
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</tbody>
</table>

ICU, intensive care unit; LOS, length of stay; NRS (R/D), numeric rating scale at rest and deep breath.
to 2.42 µg/mL in our research. The ropivacaine concentra-
tion did not exceed 4.3 µg/mL, and there were no systemic
toxicity symptoms through the monitoring of BIS and ECG
(abnormal brain electrical waves and malignant arrhythmia)
during the perioperative period. Postoperative NRS at rest
and deep breath within 48 hours and other recovery out-
comes are presented in Table 2. Two patients complained
of pain at the drainage site, and three patients endured mod-
erate to severe pain within 48 hours.

Discussion

Our research proved that PIFB combined with RSB, a
total injection of 70 mL 0.3% ropivacaine, is safe in cardiac
surgery. The peak total arterial ropivacaine concentration
varied from 0.67 to 2.42 µg/mL and no systemic toxicity
symptoms arose during the perioperative period.

Ropivacaine is a long-acting local anesthetic belong-
ing to amide group and has been widely used in clinical
situations due to its sensorimotor differentiation blockage
and enhanced safety [7]. Actually, all local anesthetics
present certain toxicity, and the toxicity correlates with their
lipophilicity [8]. Ropivacaine may possess less cardio-
vascular and central nervous system toxicity than bupiva-
caine. However, both bupivacaine and ropivacaine inhibit
SCN5A-encoded cardiac Na⁺ channel in the same mode of
action, and the modest variations in cardiotoxicity between
two drugs are associated with dosages used in clinical set-
tings [9]. In addition, in the isolated rat heart, lipid emul-
sion improves recovery from bupivacaine rather than ropi-
vacaine induced cardiac arrest [10]. Therefore, we must re-
main cautious about ropivacaine-induced systemic toxicity,
especially when a large volume of ropivacaine is applied in
patients undergoing cardiac procedures.

This study confirms that PIFB combined with RSB
is safe in cardiac surgery, and the peak total arterial ropi-
vacaine concentration varied from 0.67 to 2.42 µg/mL. It
has been reported that the mean plasma concentration of
 ropivacaine for neurological symptoms after intravenous
infusion of ropivacaine in healthy volunteers is 4.3 and 2.2
µg/mL (arterial and venous) [11]. Whether nervous and car-
diac symptoms would emerge at the same time are uncer-
tain when ropivacaine is absorbed from tissues rather than
intravenously injected, as central nervous system stimula-
tion produces initial cardiovascular activation. However,
in this study, the ropivacaine concentration did not exceed
4.3 µg/mL, and there were no nervous or cardiac toxicity
symptoms in any patients from the perspective of BIS and
ECG.

No adverse events occurred when ropivacaine plasma
concentration remained below toxic concentrations [12],
and such a finding is not surprising. Torup and colleagues
performed bilateral transversus abdominis plane blocks
with 40 mL 0.5% ropivacaine, and one-third of partici-
pants had venous ropivacaine concentration values above
2.2 µg/mL. The highest ropivacaine concentration was 5.1
µg/mL, while only one patient had a small drop in arterial
blood pressure [13]. Other trials observed that total ve-
nous ropivacaine concentration increased from 2.39 to 6.08
µg/mL during long-term epidural ropivacaine infusion, and
even a value of 7.1 µg/mL was reported with no evidence
of systemic toxicity events [14,15]. An experimental ani-
mal model draws a similar conclusion that it is not related to
adverse electrophysiological or hemodynamic effects when
ropivacaine concentration reaches potentially toxic levels
[16]. In some cases, it is difficult to justify the correlation
between local anesthetic concentrations and signs of sys-
temic toxicity. This kind of relationship is multifactorial
and influenced by individual conditions, such as anatomy
and physiological state [17].

Many methods have been attempted to address chest
tube pain, such as injections of local anesthetics into pleu-
ral or mediastinal drains, and even the application of lido-
caine to chest tubes can relieve pain after cardiac surgery
[18,19]. Several complications have been reported follow-
ing these methods, including infection, pneumothorax, sys-
temic absorption, and even ventricular standstill [20]. RSB
targets upper abdominal postoperative analgesia and can
solve chest tube related pain definitely and safely. In our
study, only two patients complained of pain at chest tube
site, which proved that PIFB combined with RSB is effective
to offer better analgesia after cardiac surgery, meanwhile,
it is relatively safe.

There are some limitations in this study. First, the
sample size was small. Our study is merely exploratory to
evaluate the safety of large volume fascial blocks in cardiac
surgery patients. Although ten patients were enrolled, all
ropivacaine concentration values were lower than the toxic
thresholds. Second, PIFB and RSB were performed after
induction to relieve patients’ discomfort. Successful blocks
were estimated by opioids and hemodynamics, not the def-
inite sensory range of patients. While all regional blocks
were finished under ultrasound, and spread of drugs was
precisely observed.

Conclusions

We demonstrated that combined fascial plane blocks
(PIFB & RSB) with a total injection of 70 mL 0.3% ropi-
vacaine do not give rise to toxic levels, and PIFB combined
with RSB is an effective and safe analgesic protocol for car-
diac surgery patients.

Abbreviations

ASA, American Society of Anesthesiologists; AVR,
aortic valve replacement; CABG, coronary artery by-
Heart Surgery Forum
pass grafting; CPB, cardiopulmonary bypass; EF, ejection fraction; ICU, intensive care unit; LOS, length of stay; MVR, mitral valve replacement; NRS, numeric rating scale; PCIA, patient controlled intravenous analgesia; PIFB, pecto, intercostal fascial block; RSB, rectus sheath block.

Availability of Data and Materials

Datasets used for this study are available by the authors upon appropriate request.

Author Contributions

LJ and YF contributed to the study design and analysis. LW and BL performed the experiments and wrote the manuscript. BJ and YS assisted in the recruitment of participants and performed the statistical analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of it.

Ethics Approval and Consent to Participate

This research was approved by Ethical Review Committee of Peking University People’s Hospital (2022PHB179-001). Written informed consent was obtained from all the patients.

Conflict of Interest

The authors declare no conflict of interest.

References


[17] Rosenberg PH, Veering BT, Urmej WE. Maximum recommended doses of local anesthetics: a multifactorial concept. Re-
