Author's response to reviews

Title: Epidural anesthesia and postoperative analgesia with ropivacaine and fentanyl in off-pump coronary artery bypass grafting

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Author's response to reviews:

Dear Editor and Reviewers,

Thank You for positive criticism and the opportunity to re-submit a revised manuscript for consideration.

In the following, we respond point-by-point the Reviewers’ comments, indicating, when appropriate, page (P) and line numbers (L) in the marked-up version of the revised manuscript.

Reviewer 1.

Dear Dr. Ishiyama,

Thank You so much for spending Your time to comment on our paper.

Major Compulsory Revisions

General Comments

1. In this study, most of the parameters showed small differences among the three groups, and statistically significant differences, which were shown in Table 2 and 3, may be clinically insignificant. An obvious difference was that patient-controlled epidural anesthesia shortened the time to extubation. Nevertheless, epidural anesthesia required inotropes/vasopressors and colloids during the operation. I suppose this study proved epidural analgesia had little efficacy on OPCAB.

We agree with Reviewer that the role of epidural anesthesia and analgesia in OPCAB is unequivocal and have indicated this in the revised Discussion (P12-14). However, both our results and most data of other authors confirm the beneficial effect of this method for respiratory function.

2. Authors described that thoracic EA with ropivacaine/fentanyl stabilizes hemodynamics (Abstract), however, epidural anesthesia decreased mean arterial blood pressure (MAP) during OPCAB.

We have changed the text of Abstract to clarify our findings (P2, Results and
Conclusion. However, we would like to mention that the vasodilatory effect of epidural blockade can be valuable for the patients with arterial hypertension that is observed frequently among OPCAB patients.

3. Authors described that thoracic EA during OPCAB prevents lung fluid accumulation (Conclusion), however, there were no intergroup differences in extravascular lung water index (EVLWI) among the three groups. The data indicated that lung fluid accumulation could be comparable among Control, EI, and PCEA groups.

During OPCAB, EVLWI did not change in both epidural groups but increased as compared to baseline during fixation of the heart in the control group (Table 2), thus epidural anesthesia has prevented the rise in EVLWI. We have mentioned these only intragroup differences in the Discussion (P12; L20-25).

4. Authors described that epidural administration of ropivacaine/fentanyl improves myocardial performance (Conclusion). However, cardiac index, cardiac function index, systemic vascular resistance index, global end-diastolic volume index, left ventricle contractility index, and global ejection fraction were comparable among Control, EI, and PCEA groups. Although central venous pressure showed statistically significant differences among the groups, the differences could be clinically insignificant (Control versus EI; 14 versus 16.8 mmHg, 11.8 versus 14.4 mmHg, 12.7 versus 14.9 mmHg). The data indicate that myocardial performance should be similar in the three groups.

We agree with Reviewer that the differences in CVP could be clinically insignificant. The study algorithm (Figure 1) was aimed to maintain the target values of cardiac index and global end-diastolic volume in all groups, thus these variables did not differ significantly between the groups and their intragroup changes were similar as well. However, as shown in Table 2, global ejection fraction in the control group decreased from baseline by 15% at the fixation of the heart and at the end of surgery, whereas increased in the PCEA group after the start of coronary flow. Moreover, dPmax, reflecting the contractility of the left ventricle, increased postoperatively only in both epidural groups. These effects are discussed in the paper (P12-13) and could reflect improvement of myocardial performance during epidural anesthesia and analgesia.

5. Authors described that epidural administration of ropivacaine/fentanyl provides adequate analgesia (Conclusion). However, VAS scores were within 20 mm at rest and 30 mm during coughing in all groups without intergroup differences (Results). Adequate postoperative analgesia was provided not only by epidural analgesia but also by intravenous fentanyl. Epidural anesthesia may have little advantage regarding postoperative pain relief.

We have modified our Conclusion according to Your comment, indicating the similar level of analgesia for all groups (P14). According to our protocol, postoperative analgesia was administered by the attending physician, who adjusted the infusion rate of analgesics aiming at a VAS score of <30 mm at rest. Thus, the same level of pain control was achieved by different methods and different doses of analgetics that led to different cardiopulmonary effects.
described in our paper. However, during analysis of our VAS data for all the study stages (Table 4), we revealed that at 12 h the VAS score was significantly lower in the PCEA group as compared to controls. This finding is also discussed in the revised manuscript (P13; L14-17).

6. Authors described that EI combined with PCA is associated with improved oxygenation (Discussion, first paragraph). Table 3 shows that oxygenation was well preserved in all groups. Statistical difference was prominent only one point (18 hours). From those results, I do not think EI combined with PCA is associated with improved oxygenation.

We have emphasized the transient pattern of improved oxygenation in the Discussion (P11:L19).

Specific Comments

1. Page 5, Line 19-20; Anesthesia was maintained with propofol 3-5 mg/kg/h and fentanyl 2-4 µg/kg/h. How did authors determine the doses of propofol and fentanyl? Did infusion rate set according to MAP or heart rate? Was bispectral index measured?

In the revised paper, we have indicated that anesthesia was maintained with propofol 3-5 mg/kg/h and fentanyl 2-4 µg/kg/h, aiming at heart rate within 50-90 beats/min and mean arterial pressure within 60-80 mm Hg (P5; L22-23). We did not use BIS-monitoring in this study.

2. Page 6, Line 16-18; Fentanyl infusion rate at 3-8 mL/h is an obscure explanation. Was initial intravenous infusion rate different in each patient? Was infusion rate changed according to the severity of postoperative pain?

The initial infusion rate was 3 ml/h. You are right; we changed the infusion rate according to the severity of postoperative pain. In the control and the EI groups, postoperative analgesia was administered by the attending physician, who adjusted the infusion rate of analgesics beginning from 3 mL/h and aiming at a VAS score of <30 mm at rest (P7; L10).

3. Page 6, Line 20-21; If blood or cerebrospinal fluid had been drawn from the epidural catheter, was operation postponed?

In our study, there were no cases of dural puncture or epidural hemorrhage, and we fulfilled aspiration probe after placement of the epidural catheter. In clinical practice, in these cases we usually change the level of epidural puncture.

4. Page 6, Line 23-Page 7, Line 3; After induction of anesthesia, the thoracic epidural injection with ropivacaine and fentanyl was made to obtain blockade of pain at Th1-6. How did authors verify the block level of Th1-6 though the patient had already slept by general anesthesia?

Thank you for the correction, we have changed this sentence (P7:L1)

5. Page 6, Line 23-Page 7, Line 3; Was initial epidural infusion rate different in each patient? Was infusion rate changed according to the severity of postoperative pain?
In the control and the EI groups, postoperative analgesia was administered by the attending physician, who adjusted the infusion rate of analgesics beginning from 3 mL/h and aiming at a VAS score of <30 mm at rest (P7; L10).

6. Page 8, Line 7-9; Who assessed the severity of postoperative pain and the level of sedation?
These assessments have been made by attending physicians (P8; L9-11).

7. Figure 1; Please clarify the dose of phenylephrine, ephedrine, and nitroglycerin. If MAP higher than 80 mmHg occurred, were infusion rates of propofol and fentanyl changed? Depth of anesthesia should be one of the important factors for maintaining MAP.

We have clarified this issue in the Figure legend: During anesthesia, this algorithm was used to correct HR and MAP only if the doses of propofol 3-5 mg/kg/h and fentanyl 2-4 µg/kg/h were unable to maintain HR within 50-90 beats/min and MAP within 60-80 mm Hg. For perioperative management, we used the following doses of intravenous agents: ephedrine 5-10 mg, phenylephrine 0.05-1 mg, nitroglycerin 0.3-3 mg/h and furosemide 10-20 mg.

8. Discussion; Please rewrite according to the results.
We have made several changes in Discussion in light of Reviewers’ comments (P11-14).

Reviewer 2.
Dear Dr. Reuter,
Thank You very much for spending Your time for a work with our manuscript.

1. You point out as major finding of your study the improvement of gas exchange and the resulting shortening of duration of mechanical ventilation. Please provide those data (you only mention that there was a reduction in the PCEA group of 32 %, and a tendency to decrease in the EI group).

The data regarding duration of mechanical ventilation are provided in Table 1. We have indicated this in the revised text (P9; L25). The data regarding gas exchange are shown in Table 3, respectively.

2. Please comment on the clinical relevance of this shortening.
The decrease in duration of mechanical ventilation is one from clinical outcomes that can influence the course of postoperative period and can be used for the evaluation of perioperative therapy. In ICU patients, prolonged weaning is an independent risk factor for longer ICU stay and hospital mortality [Tonnelier A. et al., Respir Care 2011;56:583-90]. After cardiac surgery, early tracheal extubation is a part of the fast-track concept aiming to avoid or reduce complications and achieve cost-savings [Myles PS, McIlroy D. SeminCardiothoracVascAnesth 2005;9:5-16]. We have emphasized this issue in Discussion (P14; L3-6).

3. What is your explanation that those beneficial effects can be seen only in the PCEA group, and not (statistically relevant) in the EI group? The management
perioperatively was the same for the EI and PCEA group. The difference must then be the postoperative management. PCEA will potentially optimize pain therapy. So please provide these data. Was additional pain medication besides EI, or besides EI+PCEA necessary? Was there a difference in use between those two groups, or compared to the control group?

We absolutely agree with you that the difference in results between the PCEA and the EI groups is caused by the postoperative management and individualized pain therapy in the PCEA group that also influenced positively the cardiorespiratory functions. As you have requested, we provided the data regarding VAS in studied groups in Table 4 of the revised paper. We have revealed that at 12 h the VAS score was significantly lower in the PCEA group as compared to controls. This finding is also discussed in the revised manuscript (P13; L14-17). Since the epidural blockade at Th2-4 level provides pain control only for sternotomy, in most cases the OPCAB patients require additional analgesia using NSAID for the pain caused by operation on lower extremity for harvesting v. saphena and on upper extremity for harvesting a. radialis for the grafts. For these purposes, we used lornoxicam at a fixed dose of 8 mg IV before OPCAB and every 12 h during two postoperative days (Methods, P6; L14-16); there were no intergroup differences in its’ administration.

4. When and how often was the VAS assessed? It is interesting that you did not find a difference here between the groups. This equality would be moreover an argumentation to skip the concept of EI or EI+PCEA in cardiac surgery procedures.

As we have indicated in Methods, the severity of postoperative pain at rest and during coughing was assessed with VAS score at 6, 12, 18, and 24 h after OPCAB (P8; L9-10). The finding that VAS scores were within 20 mm at rest and 30 mm during coughing in all groups without intergroup differences is explained by the design of our study. According to our protocol, postoperative analgesia was administered by the attending physician, who adjusted the infusion rate of analgetics aiming at a VAS score of <30 mm at rest. Thus, the same level of pain control was achieved by different methods and different doses of analgetics that led to different cardiopulmonary effects described in our paper. However, as we have already indicated in previous answers, during analysis of our VAS data for all the study stages (Table 4), we revealed that at 12 h the VAS score was significantly lower in the PCEA group as compared to controls. This finding is also discussed in the revised manuscript (P13; L14-17).

5. Did you assess a potential motor blockade caused by ED, e.g. Bromage score? If so, please report.

In this study, we did not assess the potential motor blockade caused by epidural blockade to shorten the time between epidural catheterization and start of anesthesia induction.

With the above changes, we have complied with the critiques and most comments. In our opinion, the manuscript has improved from the revision, and we hope it will be accepted.
On behalf of all the authors,

Yours sincerely

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