**Author’s response to reviews**

**Title:** Observations on significant hemodynamic changes caused by high concentration of epidurally administered ropivacaine: Correlation and prediction study of stroke volume variation and central venous pressure in thoracic epidural anesthesia

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**Version:** 2  **Date:** 20 Sep 2017

**Author’s response to reviews:**

We really appreciate with your kind and detailed comments to our study. We tried to revise our manuscript in concise way as your comments. And our manuscript was revised through authorized English language editing service again.

Reviewer 1)

1. Abstract

Results: 109 patients were analyzed. MAP and systemic vascular resistance index were significantly decreased and SVV was significantly increased after epidural loading only in 0.75% ropivacaine group. Significantly profound hypotension was found in aged patients.

A) Thank you for your good comment. We corrected the result of abstract as your comment.

Revised manuscript is following.
Data from 109 patients were analyzed. MAP and systemic vascular resistance index were significantly decreased and SVV was significantly increased after epidural loading only in the 0.75% ropivacaine group. There was a significant difference in hemodynamics between young and elderly subgroups in 0.75% ropivacaine group.

2. Methods:

The first and second paragraphs should be written by a more concise, non-repeated way.

A) Thank you for your smart opinion. We removed the repetition and combined the two paragraphs.

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This study was registered with Clinicaltrials.gov (NCT01559285). After approval by the IRB of the Yangsan Hospital of Pusan National University, this prospective, randomized, and double-blind study was carried out in 120 patients, 18 to 65 years of age, undergoing major upper abdominal surgery using combined TEA and general anesthesia after obtaining informed consent. Medical histories and physical examinations were obtained for all subjects before admission into the study. Exclusion criteria included: known significant cardiac or respiratory disease, cardiac arrhythmia, neurological dysfunction, or a contraindication for regional anesthesia. The patients were randomized to receive one of three different concentrations of the study solution in 8 ml: 0.75% ropivacaine (60 mg), 0.375% ropivacaine (30 mg), or 0.2% ropivacaine (16 mg). Random numbers were generated by a computer and used to allocate the subjects into their groups. The allotment took place after induction of anesthesia. The study solution was prepared and blinded by an anesthetic nurse investigator, and therefore, the induction anesthesiologist was unaware of the drug concentration.

3. Results

Results: please rewrite and organize the results.

A) Thank you for your detailed comments. We corrected the results in a concise way as your comments.

- The first paragraph: The consort flow diagram was shown as in figure 1. 109 patients were included for analyze. The demographic data and anesthetic data were shown in Table 1 and there were non-significantly differences among three groups. You do not have to repeat the data in the manuscript.

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The Consort flow diagram is shown in Figure 1. A total of 109 patients were included for analysis. The demographic data are shown in Table 1 and there were no significant differences among the three groups. BIS and end-tidal sevoflurane concentration also showed no significant differences among the groups.

- The second paragraph: In 0.75% ropivacaine group, there were significantly decreased MAP, SVRI, and significantly increased SVV than those in 0.375% and 0.2%.

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In the 0.75% ropivacaine group, there was significantly decreased MAP, SVRI, and significantly increased SVV compared with those in the 0.375% and 0.2% groups.

- The 4th paragraph: just show your results, for example, the time course of hemodynamic and parametric changes was shown as in figure 2. Significant changes were observed at T10 (10 minutes after loading).

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The time course of hemodynamic and parametric changes is shown in Figure 2. Significant changes were observed at T10 (10 minutes after loading).

- The 5th paragraph: we also analyze the differences in hemodynamic changes in young (<60 y/o) and old (>60 y/o) patients in each group as shown in Table 2. I do not think "interesting" is optimal in the results.

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We also analyze the differences in hemodynamic changes in young (<60 years) versus elderly (>60 years) patients in each group as shown in Table 2. In the 0.75% ropivacaine group, there were significant differences in CVP, SVV, SVRI, and SVI between the young and elderly subgroups.

- The 6th paragraph: correlation between parameters was shown as in table 3.

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The correlations between parameters are shown in Table 3. MAP showed a negative correlation with SVV and a positive correlation with SVRI.

The 7th paragraph: as in previous paragraph, it is not necessary to repeat results in the manuscript.

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Hemodynamic data comparing responders (20% decrease in MAP) and non-responders are shown in Table 4 and the ROC curve for performance of SVV and CVP in predicting hypotension is shown in Figure 3. Although SVV increased in the responder group, SVV was not a strong enough predictor of hypotension.

4. Discussion

4-1. The first paragraph: I suggest the authors to start with a simple way such as

The main results in our study are: 1) Significantly decreased MAP after epidural administration of ropivacain was observed only with 0.75% but not with 0.375% and 0.2% ropivacain. 2) Reduction of SVR, increase of SVV, but not changes on CVP, were significantly correlated with decrease of MAP. 3) hypotension in the high concentration group was more prevalent in aged patients, and the accompanying SVV changes were more pronounced. 4) despite significantly correlated with MAP changes, SVV was found to be a weak predictor of hypotension following TEA.

A) Thank you for your detailed comments. I corrected the first paragraph as your comments.

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In our study, we found the followings: 1) Significantly decreased MAP after epidural administration of ropivacaine was observed with 0.75% compared with 0.375% and 0.2% ropivacaine, 2) A reduction in SVR and an increase in SVV showed a significant correlation with a decrease of MAP, but CVP did not, 3) In elderly patients, hypotension in the high concentration group was more prevalent and the accompanying SVV changes were more pronounced, 4) SVV was found to be a weak predictor of hypotension following TEA although it showed a significant correlation with MAP changes.
4-2. How about to rewrite the discussion based on the authors' results in a concise and precise way? I suggest the authors to have a brief conclusion with clinical impact on each paragraph.

**discussion**

Firstly, I think the results agree with that "hypotension after TEA is mainly associated with deeper sympathetic blocks but not decreased stroke volume" by the changes of MAP, SVRI and SV. Please give the readers a conclusion with clinical impacts, such as 0.75%, but not concentrations below 0.375% ropivacain, administered epidurally with general anesthesia may associated with significant hypotension, especial on patients aged more than 60. The increase of SVV, but not changes in CVP, is significantly correlated with development of hypotension. Though SVV is found not a strong enough predictor of hypotension after TEA, we still recommend the cutoff value of 9.5%.

A) Thank you for your excellent comments. We rewrote and reconstructed the discussion and conclusion as your comments. And we tried to add a brief conclusion with clinical impact on each paragraph. We shaded it in following manuscript.

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In our study, we found the followings: 1) Significantly decreased MAP after epidural administration of ropivacaine was observed with 0.75% compared with 0.375% and 0.2% ropivacaine, 2) A reduction in SVR and an increase in SVV showed a significant correlation with a decrease of MAP, but CVP did not, 3) In elderly patients, hypotension in the high concentration group was more prevalent and the accompanying SVV changes were more pronounced, 4) SVV was found to be a weak predictor of hypotension following TEA although it showed a significant correlation with MAP changes.

Hypotension is documented to be most common adverse effect after epidural administration of ropivacaine [10]. Hypotension occurs 5-20 min after the administration of epidural loading. The incidence of hypotension was significantly different depending on the concentration of ropivacaine; 54.6%, 49.2%, and 38.7% in 1%, 0.75%, and 0.5% of ropivacaine, respectively in the Food and drug administration (FDA) report. In our data, the incidence of hypotension was 61.2%, and a marked decrease in MAP was observed in 0.75% ropivacaine group compared to the other concentration groups. Some studies have reported conflicting results. Ginosar and colleagues did not find any differences between the groups administered 0.5% and 0.25% bupivacaine [6]. Dernedde and colleagues also observed that a 0.5% levobupivacaine group showed no statistically significant difference in hemodynamic parameters compared to 0.15% levobupivacaine, which was a much lower concentration than that used in our study [11]. Liu and colleagues also suggested that episodes and severity of hypotension and orthostatic changes in systolic blood pressure or heart rate were equivalent among the groups administered different concentrations of ropivacaine [12]. They investigated 0.05%-0.2% of ropivacaine with fentanyl during the study. We assumed that different concentrations and types of LA, site of blockade, and the combination with general anesthesia might cause these differences. Thus we should be aware that hypotension may occur in patients administered 0.75% ropivacaine epidurally during general anesthesia.
To date, hemodynamic changes after epidural anesthesia have been shown to be affected by various factors. The width of sympathetic denervation, balance of sympathetic and parasympathetic activity, pharmacological effect of systemically absorbed LA, and distribution of circulatory blood volume following epidural anesthesia should be taken into account when considering the hemodynamic effects of epidural anesthesia [6, 13-15]. Low thoracic epidural anesthesia (T5-L4), similar to our study, induces hypotension mainly by peripheral sympathetic blockade with block of the splanchnic fibers, whereas high thoracic epidural anesthesia (T1 to T5) induces hypotension by block of the cardiac afferent and efferent sympathetic fibers with loss of chronotropic and inotropic drive to the myocardium.

A reduction of MAP was regarded owing to a decrease in SVR. However, few clinical studies have investigated the change in SVR under TEA. Since the sympathetic blockade occurring after epidural anesthesia causes compensatory vasoconstriction of capacitance vessels of mesentery and lower extremity, it is difficult to study the change of SVR following TEA. In our study, we demonstrated a significant decrease of SVRI and accompanied decrease of MAP following epidural administration of 0.75% ropivacaine. But, we could not observe the difference in SVI and HR among the groups. Therefore more decrease of MAP in 0.75% ropivacaine was supposed to be a result of a more decrease in SVR by deeper sympathetic blockade, but not negative inotropic and chronotropic effect.

SVV, the variation in left ventricular stroke volume between the inspiratory and the expiratory phase during positive-pressure ventilation, is considered to be a good indicator of fluid responsiveness in the intensive care unit (ICU) and the operating room [16]. In our result, the elevation of SVV was accompanied by the decrease of SVRI, which was remarkable in 0.75% ropivacaine group. On the correlation analysis, SVV correlated negatively with MAP and positively with SVRI, not with CVP. Therefore, we can assume that increased SVV are the result of decreased SVRI by sympathetic blockade. In this case, increased SVV means functional hypovolemia and use of vasopressor could be preferable, not the volume expansion for the correction of accompanying hypotension.

The subgroup analysis demonstrated that hypotension in the high concentration group was more prevalent in elderly patients, and the accompanying SVV changes were more prominent. Therefore we can assume that a high dose of ropivacaine (0.75%) in elderly patients caused the increase of the block width and thus the hemodynamic effect of TEA was exaggerated. Previous many studies concerning the effect of age on spread after TEA documented segmental dose reduction is required with increasing age after TEA [17-20]. In addition, Stephen et al. described decrease in MAP after epidural lidocaine administration was significantly more in elderly patients [19]. The mechanism of increased block width in older patients is presumed to be a decreased egress of injected fluids via neural foramina in aged patients and increased susceptibility due to decrease in the number of myelinated nerve fibers and general deterioration of the mucopolysaccharides. It is assumed that increased susceptibility is also associated with prominent response at high concentrations in our study. In addition, SVI and HR in 0.75% group was significantly lower in elderly patients. We assumed that extended blockade to high thoracic level might cause negative inotropic and chronotropic effect in elderly patients. Another suspected mechanism is due to non-compliant heart of elderly patient [21]. Even small change in
venous return will cause large change in ventricular preload and SV in non-compliant heart. Therefore we suggest that high concentration of ropivacaine should be avoided in elderly patients during TEA.

A few studies have reported SVV is a useful predictor of potential hypotension during the early postoperative period following a combination of general and epidural anesthesia. However, the reliability of SVV could still be an issue and needs to be further investigated during TEA. Kobayashi and colleagues suggested that SVV could predict fluid responsiveness in patients undergoing surgery with OLV (AUC: 0.900, optimal threshold value: 10.5%) [22]. Xu and colleagues also suggested that SVV could be an accurate indicator (AUC: 0.86, optimal threshold value: 13%) [23]. In our data, SVV was acceptable as an ancillary prediction tool (AUC, 0.687) and the optimal threshold to differentiate between responders and non-responders was 9.5% (sensitivity of 60.6% and specificity of 68.9%). However, according to a reported guideline for accuracy of a diagnostic system, the AUC should be above 0.7 [24]. Thus it could be considered weak as an indicator to predict subsequent hypotension in our study.

Our study has several limitations. First, the use of ephedrine during the study period for protection against possible adverse events following hypotension might mask the hemodynamic effect caused by epidurally administered ropivacaine. We analyzed the consumption and incidence of ephedrine used to correct for bias. The consumption of ephedrine was highest in the 0.75% ropivacaine group. Therefore, we thought a decrease of MAP and SVR might be more significant in the 0.75% ropivacaine group if ephedrine was not used. Although SVV could be affected by the use of vasoactive drugs such as ephedrine, Hadian reported that increasing inotropes or vasoconstrictors did not change SVV [25]. Therefore, the effect of ephedrine on SVV could be limited. Second, we did not assess the height of the epidural blockade because the study solution was administered during general anesthesia. Third, we did not show the hemodynamics at a fixed dose at a different concentration to determine the concentration effect on hemodynamics following TEA. We could not perform the study at a fixed dose because a high volume was needed to meet the 0.75% ropivacaine (60 mg) dose at a low concentration. We considered that the administered volume of LA could be an influencing factor on the block height and following hemodynamics in TEA. Additionally, other factors that could affect SVV such as intra-abdominal pressure, basal intra-vascular volume status, and intrinsic chance of error of SVV were not considered.

Conclusions

In this study, we found that a concentration of 0.75% but not that below 0.375% of ropivacaine, administered epidurally with general anesthesia may be associated with significant hypotension, especially in patients older than 60 years. Therefore, care should be taken to prevent significant hypotension when epidural analgesia is performed with 0.75% ropivacaine under general anesthesia in elderly patients. An increase in SVV, but not changes in CVP, is significantly correlated with the development of hypotension. Although SVV was not found to be a strong predictor of hypotension after TEA, we still recommend a cutoff value of 9.5%.

Reviewer 3)
1. Introduction

- pp 13-15: The sentence is partially correct. Put precise references.

A) Thank you for accurate comment. We checked the references. There were indirect and unmatched references in our references. Therefore we changed them to be more precise references.

Revised references are following


- Please specify the clinical message that the authors want to send

A) We wanted to know whether hypotension following TEA is more significant when higher concentration (0.75%) of ropivacaine is administered. And, we wanted to know whether the SVV could be a diagnostic tool for detection of hypotension after TEA with combined general anesthesia. Therefore, we changed “hemodynamic derangement” to “hypotension” to specify the message.

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In the current study, we tested whether hypotension following TEA is more significant when using a higher concentration of LA, which was administered to patients undergoing major upper abdominal surgery. Additionally, we evaluated whether SVV could be a diagnostic parameter for detection of hypotension after TEA combined general anesthesia.

3. Materials and Methods

- The inclusion criteria are: 18 to 65 years old

On clinical trials.gov is not illustrated subgroup analysis (two groups at the age of 60): please add

A) s Thank you for your good comment. We added the subgroup analysis during previous revision process not at first. We added the analysis on clinical trial.gov and we attach the file.
Sample size calculation: It is incorrect to make the calculation from personal data. Use the data of scientific literature.

A) We totally agree with your opinion. However, unfortunately, we could not find the data of literature when we started this study. So we used data from our preliminary data.

4. Discussion

please specify the clinical message that the authors want to send. It is not clear. How can you use your results in the daily clinical particle?

A) We found that 0.75%, but not concentration below 0.375% ropivacaine, administered epidurally with general anesthesia may associated with significant hypotension, especially on patients aged more than 60. Therefore, the first clinical message is that we should be careful of significant hypotension when we perform epidural analgesia with 0.75% ropivacaine under general anesthesia especially in elderly patients. And second clinical message is the performance of SVV for hypotension following TEA. SVV was significantly correlated with development of hypotension. Although SVV was not strong enough to be a predictor of hypotension, we think the cutoff value of 9.5% could be still helpful.

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In this study, we found that a concentration of 0.75% but not that below 0.375% of ropivacaine, administered epidurally with general anesthesia may be associated with significant hypotension, especially in patients older than 60 years. Therefore, care should be taken to prevent significant hypotension when epidural analgesia is performed with 0.75% ropivacaine under general anesthesia in elderly patients. An increase in SVV, but not changes in CVP, is significantly correlated with the development of hypotension. Although SVV was not found to be a strong predictor of hypotension after TEA, we still recommend a cutoff value of 9.5%.