

Dear Editor-in-Chief, Lian-Sheng Ma and Science Editor, Ze-Mao Gong,

Thanks for your responses and giving us the opportunity for revision regarding our manuscript, NO: 28627, entitled “Influence of capsaicin infusion on secondary peristalsis in patients with gastroesophageal reflux disease”. We have made appropriate corrections and changes in points according to the reviewers’ suggestions. We have modified the text where appropriate. Our responses and changes are enclosed herewith. We look forward to hearing from you soon.

Best regards,

Dr Chien-Lin Chen, MD, PhD

Reviewer 1

1. Congratulation for the quality of the work. I questioned the suppression of the cephalic phase of gastric secretion since the pharynx was by-passed.(Pavlov's esophageal fistula dog).I think that this aspect should be remarked in the conclusions

Response: We thank for the comment of the reviewer. We have revised the discussion according to the comment of the reviewer.

Reviewer 2

1. Many patients with GERD have ineffective esophageal motility. How many patients had no secondary peristalsis even by air injection into the esophagus?

Response: We thank for the comment of the reviewer. In our prior work (Journal of Gastroenterology and Hepatology **29** (2014) 296–300, we have shown that the prevalence of failed secondary peristaltic response during slow air injection was 27-57%. However, in this study, up to 7 patients had no secondary peristalsis after saline infusion.

2. This study revealed some physiological response for capsaicin administration. However, many patients did not tolerate the study protocol. Thus, I think that this study cannot indicate clinical implication. Moreover, repetitive capsaicin administration on GERD patients must be dangerous although it made desensitization in GERD patients who could tolerate the study protocol.

Response: We agree with the concern of the reviewer. The protocol and its safety had been approved by the Research Ethics Committee of the hospital. This study may provide the physiological evidence of capsaicin sensitization in patients with GERD more than the clinical implication, since the sample size in this study is too small. We have acknowledged this as the limitation of this study.

Note: P14, the 2nd paragraph.

3. During slow injection patients might have primary peristalsis. How did you calculate the threshold volumes of eliciting secondary peristalsis when primary peristalsis occurred during slow injection?

Response: The protocol we used has been consistent and reported in our previous work. In condition when primary peristalsis occurs during slow air injection, secondary peristalsis will not be counted. In addition, this work never encountered

any of primary peristalsis during air injection, since we request the patients not to swallow during air injection.

4. Capsaicin administration did not alter the amplitude of secondary peristalsis, which was different from your previous study with healthy subjects. How do you explain this different finding?

Response: Thank for the comment of the reviewer. We have acknowledged this comment by adding a paragraph in the discussion. *The discrepancy in the amplitudes of secondary peristalsis after capsaicin infusion between healthy controls and GERD patients can be explained due to the fact that patients with GERD are more likely to have relatively poor motility in term of ineffective motility. In patients with abnormal primary peristalsis, abnormal secondary peristalsis has been observed (Schoeman MM et al, Gut 1995;36:499-504). It is suggested that the defect may occur in the efferent part of the motor pathway.*

Note: P13, Line 1-4 from the bottom; and P14, Line 1-2 from the top.

Minor comments

1. “Infusion of capsaicin increased the number of GERD patients with successive secondary peristalsis during slow air injection than saline infusion (P=0.001)(Figure 3A), but the difference was not shown between first and second capsaicin infusions (P=0.18)(Figure 3B)” should be “Infusion of capsaicin increased the number of GERD patients with successive secondary peristalsis during slow air injection than saline infusion (p=0.001)(Figure 3A), but the

difference was not significant between first and second capsaicin infusions
($p=0.18$)(Figure 3B)”

Response: Thank you for pointing out the error when preparing the manuscript. We have corrected it.

Note: P10, the 2nd paragraph.