

To: The Editor, *World Journal of Gastroenterology*

Dear Sir:

Thank you for considering our manuscript, **ESPS Manuscript NO: 14422**
“Pathophysiology of functional heartburn based on Rome III criteria in Japanese patients”. We have responded to the reviewers’ comments and criticisms, provided point-by-point responses and have corrected the manuscript accordingly to conform to the requirements of the Editorial Office. Regarding the reviewers’ comments, please see the attached sheets.

We hope that our manuscript will now be deemed acceptable for publication in the *World Journal of Gastroenterology*. Thank you in advance for your time and attention. We are sorry for revising our manuscript near the deadline.

Sincerely,

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Reply to Reviewers' comments

Reviewer 1: Comments to the Author

Major comments

1. The Authors defined refractoriness on the basis of the lack of response to a single PPI dose. Perhaps the use of a double PPI dose would have been more suitable and rigorous to identify therapeutic failure
2. It is not clear which normal values for impedance-pH-metry were used.
3. Why did the Authors use SI instead of SAP in order to correlate symptoms to reflux episodes? The latter parameter seems to be more reliable
4. The differences between the Authors' and the Savarino's group findings are likely related to the fact that the latter ones were obtained by studying patients out of PPIs. However, these differences should be discussed more in depth.
5. As to the proposed therapeutic regimens to be used in FH patients, the Authors should refer to a recently published review in this field (Savarino E et al, Nature Reviews Gastroenterol Hepatol 2013).

Minor comments

1. English language must be improved
2. The introduction can be shortened by 1/3

Answer to the Reviewer 1

Thank you for your extremely important advice. We agree with your comments. We answer to your comments and criticisms point-by-point.

Major comments

1. We described discussion session as the following: (from line 22, page 16 to line 23) that the dose of PPI is strictly limited under Japanese national health insurance and we never be able to use double dose of PPIs for NERD patients. So, we planned this examination to reflect the Japanese clinical practical situation strictly and to manifest the pathophysiology of PPI refractory NERD in Japan.
2. There have been no definition of normal values of 24hMII-pH metry in patients receiving PPI treatment, so we used reported value in patients not receiving PPI treatment. We described method part, from line 4, page 9 to line 10.
3. The calculation of SI with automatic analysis software is set the time interval at 5 minutes before symptom occurrence, while SAP is set the time interval at 2 minutes. It has been reported that the symptom occurrence time intervals after reflux episode is longer with non-acid reflex than acid reflux (Mainie,I. Gut 55, 2006). Further, the specialist confirmed SI under manual calculation and was easy to assess at SI rather than SAP.
4. We added discussion part as the following: (from line 15, page 16 to line 18) that “This difference may be related to the presence or absence of PPI treatment. The present analysis was undertaken to evaluate the clinical practical situation of NERD, and to identify its pathophysiology, while avoiding the acid-related effects.”
5. We added discussion session as the following: (from line 10 page 17 to line 13) “A recently published review has mentioned that the use of 24MII-pH is the only functional method to reliably perform sub-classification of the complex population of patients with NERD. In addition, this technique is recommended to clearly

separate the subsets of patients with real reflux disease from the subset with FH”
And (from line 17, page 17 to line 18) “For example, patients with FH should be treated with non-PPI and non-reflux inhibitor medication, such as with pain modulators”

Minor comments

1. We improved English language by Native speaker and attached proof.
2. We shorten the introduction part.

Reviewer 2: Comments to the Author

This manuscript deals with "Pathophysiology of functional heartburn based on Rome III criteria in Japanese patients". The manuscript is well presented and of interest. I found no problem with it and it can contribute to increase the knowledge of this topic. All parts of the manuscript are well organized, and valuable conclusions are provided.

Answer to the Reviewer 2

We really appreciated the reviewer's kind and accurate comments. We are pleased to be evaluated of our manuscript and to have a good answer.

Reviewer 3: Comments to the Author

1. Regarding the Rome foundation algorithm in the evaluation of these patients pH study is recommended before the manometry. In this study the manometry is done

first. Is this because of the national program? Is there any other reason? If any reason for this, it should be clarified clearly and also mentioned in the manuscript. ? I think that it would be interesting also to see the comparison of the clinical data and presentation of the enrolled patients with those who had been excluded because of positive manometric findings. ?

2. The study results are given mainly on the para-clinical data. One likes to have also the clinical data, namely the classical and extra-esophageal presentations as well. Did the patients have regurgitation too? Did they have upper and lower respiratory symptoms? If yes the probability of reflux disease may be predicted to be higher. ?
3. In the inclusion of the patients those who have been given a single dose PPI have been included. Shouldn't you probably go for the double dose (like omeprazole 40 mg) and then include the patients for the study, as it is recommended in the Rome foundation criteria? ?
4. Table 1 which is showing the framework of the whole group is not very useful and can be omitted, because Table 2 is sufficient and more useful. ?
5. Tables 3 & 4 can be merged as they are showing the questionnaire data. ?
6. The small numbers of patient group may be the reason for non-significant differences between the groups. ?
7. In the abstract despite the several questionnaires it is better to mention the questionnaire names. ?
8. Do you offer any clinical implication based on your study for the clinicians? Or this is mainly a study of theoretical importance?

Answer to the Reviewer 3

Thank you for your accurate comment. We agree with your comments. We answer to your comments and criticisms point-by-point.

1. According to the Rome III algorithm for diagnosis of FH, manometric study is not recommended. It means that esophageal motility disorders that have no histopathological abnormalities might be involved in FH. And we have reported that PPI-refractory NERD patients have esophageal motility disorders, and gastro-esophageal reflux plays a role in symptom onset (Izawa Digestion 89, 2014). Therefore, we firstly used manometry to exclude esophageal motility disorders from PPI-refractory NERD patients.

We have described this sentence in introduction part, (from line 6, page 6 to line 15).

2. The questionnaires of FSSG include the extra-esophageal symptoms questions and we collected these data. However, we examined total points of FSSG score for the evaluation of symptoms in this study. We should try to further examination at the reviewer's points of view in the future. Thank you for your important comments..

3. We described discussion part, (from line 22, page 16 to line 23) that the dose of PPI is strictly limited under Japanese national health insurance and we never be able to use double dose of PPIs for NERD patients. So, we planned this examination to reflect the Japanese clinical practical situation strictly and to manifest the pathophysiology of PPI refractory NERD in Japan.

4. We have omitted Table 1.

5. We have merged Table 3 and 4 and made new Table 2

6. Reviewer's comments a truly reliable. We are going to accumulate the data and reflect next investigation.

7. We added questionnaire names in the abstract section (from line 6, page 2 to line 10), “The patients also completed several questionnaires while they were receiving the PPI treatment, including the Questionnaire for the Diagnosis of Reflux Disease (QUEST), the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG), the Gastrointestinal Symptoms Rating Scale (GSRS), SF-36, and the Cornell Medical Index (CMI).”
8. We added this comment in discussion section as following; (from line 13, page 17 to line 17). “Our study supports this idea, and indicates that NERD is a markedly heterogeneous condition from the pathophysiological and clinical points of view, and that it should be correctly classified by esophageal function testing to provide adequate relief from the related symptom.” and (from line 18, page 17 to line 19). “Our data might contribute to developing a therapeutic strategy for patients with PPI-refractory NERD.”