Reviewer’s report

Title: Response of the airways and autonomic nervous system to acid perfusion of the esophagus in patients with asthma: a laboratory study.

Version: 1 Date: 30 September 2012

Reviewer: Andras Rosztoczy

Reviewer’s report:

Dear Sir,

Thank you for giving us the opportunity to review the manuscript of Dr. D Lakmali Amarasiri entitled “Response of the airways and autonomic nervous system to acid perfusion of the esophagus in patients with asthma.”

The manuscript discusses an interesting topic, although there are some questions to be answered. Therefore this manuscript may not be suitable for publication in its current form, but after the revisions suggested below.

Major comments:

1. In a recent paper Rosztóczy et al. published detailed evaluation of the pulmonary and esophageal function in patients with asthma, which includes esophageal acid perfusion test as well. Since the subject of their paper has a significant overlap with the submitted manuscript, it seems to be essential to discuss those results. In contrast to the results of this manuscript, they were unable to show significant changes in the FEV1 for esophageal acid perfusion itself: However, during combined acid perfusion + metacholine challenge asthmatic patients reached the significant FEV1 decrease at lower metacholine dose, than during the standard metacholine test. (Rosztóczy A, Makk L, Izbéki F, Róka R, Somfay A, Wittmann T. Asthma and gastroesophageal reflux: clinical evaluation of esophago-bronchial reflex and proximal reflux. Digestion. 2008;77(3-4):218-24. Epub 2008 Jul 19.)

2. methods section – page 5 – In the referred article (24) DeMeester and Johnson discussed their results obtained single channel intraesophageal pH monitoring. Why did authors applied this for their measurements obtained by the proximal pH sensor. It is well known that those parameters are not applicable for proximal reflux. What was the actual cut-off value for the determination of pathological proximal reflux in this study?

3. methods and results section – page 6 and 7 – The authors used concentrated lime juice in their experiments for the acid perfusion test. In the manuscript they write: “concentrated lime juice (pH 2-3) alternatively, at a rate of 2mL/min for 10 minutes” Why has that been chosen? Please add references! What was the actual pH (pH 2 and means 10 times higher H+ ion concentration than pH 3)? Why do they think that acidity itself and not something else is responsible for the
observed changes (lime juice has a number of components)? Furthermore, saline and lime juice looks and smells differently. How were the subjects and the examiners blinded to eliminate the obvious placebo effect? Written data in this section do not suggest double-blinded testing! Has they performed any cross over tests? Normally, acid perfusion tests require at least 2-2 infusions of acid and saline in a double blinded manner. Why did they apply 30 minutes resting period between esophageal infusions and vagal/pulmonary function testing?

4. The asthma severity of the GERD positives and negatives seems to be different. Please add additional statistics to clarify this!

5. Authors state, that the difference between the mean FEV1 values after saline and acid perfusion is 0.1L, while the standard error is 0.4L for this parameter. I can hardly believe, that the statistical evaluation would show such a high (p<0.001) level of significance. Furthermore, authors stated different SE values in the text 2.7±0.1L and 2.6±0.1L. So, which is the real SE? Please provide the exact FEV1 values of the studied patients in a separated data file for repeated statistical evaluation.

6. Control subjects were not used. Please add the following groups of controls (healthy subjects and non-asthmatic GERD patients).

Minor comments:

1. The introduction should be shortened.

2. page 5 –”Stokholm” is correctly Stockholm.

3. page 5 and 6 – please use “LES” instead of “LOS” since always “esophagus” is used in the manuscript.

4. page 6 – authors state: “The day following removal of the pH catheter, following an overnight fast, a feeding tube (4mm diameter) was used to deliver acid to the distal esophagus. The tube was inserted to 15 cm above the upper border of the lower esophageal sphincter (LES).” In fact, 15 cm above the LES should not be considered the distal but rather the middle (or the lower part of the proximal) esophagus. Later in the discussion they state the following: “In the present study, the esophageal catheter was placed at 10 cm above the LES.” So what was the real catheter position? Please clarify!

5. page 6 – authors state: “Oral asthma drugs were withheld for 24 hours and inhaled drugs for 8 hours prior to the study, allowing inhaled or nebulized beta-2 agonists on an as-required basis.” Did they exclude those patients (or at least delay their testing) who needed such medication in the last 8 hours?

6. In table 2. data shown as “mean (SE)” instead of “mean±SE”. Shince the latter form is used in other sites of the manuscript please correct!

**Level of interest:** An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.