

Peer Review File

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Reviewer A

1. Comment: Lines 98-99: "Later, the distinction...." The authors use specific terms EUCR and EURR, not used previously, and do not give a reference for these designations. Please reference this sentence

Response: Citations #14 and 15 were added 2. Narrative, paragraph number

2: The authors seem to suggest that the gas venting due to tLOSr causes EURR, but they did not reference the only manuscript that actually proves this point, i.e.Lang et al. Mechanism of UES relaxation initiated by gastric air distension. Am J Physiol 307:G452-G458, 2014.

Response: Citations #17 and 18 were added. See below: "Lang et al.17 used animal models to determine that the EUSR was temporally correlated with esophageal air stimulation after a tLOSr rather than gastric distention or the tLOSr. This temporal correlation between air reflux and EUSR has further been observed in human models.18"

3. Page 6, paragraph 1: The authors suggest that the physiological mechanism of EUCR and EURR are poorly understood, but this is false. We know the types of receptors and their location, the afferent nerve, the efferent nerve, and brainstem nucleus that controls these reflexes. We know more about these two reflexes than any other reflex mentioned in this review. Please complete the review of this issue

Response: See additions below: "The EUCR reflex is likely mediated by slow adapting mechanoreceptors in the muscular layer of the esophagus.1,25-27 This would account for why this reflex is stimulated by slow distention with liquid rather than rapid distention with air. Conversely, the relaxation reflex is mediated by rapidly adapting receptors in the mucosa only. 26,28 This is supported by studies showing an absence of UES relaxation in response to rapid distention with mucosal anesthesia.26,27 The afferent nerve both reflexes consists of the thoracic vagus, the cervical branch of the recurrent laryngeal nerve, and the superior laryngeal nerve25,26,29 Efferent nerves of these reflexes likely are the RLN and the cervical vagus, though this has not been definitively studied in humans.30 The EUCR is mediated by subnuclei of the nucleus tractus solitarii (NTS), dorsal motor nucleus, and the nucleus ambiguus in the medulla. The EURR is mediated by the NTS, nucleus ambiguus, area postrema, and dorsal motor nucleus. 31"

4. Page 6, paragraph 1, sentence 2: "The afferent fibers...." Please reference.

Response: References #25,26,29 added

5. Page 6, paragraph 1, last sentence: The authors reference 25 to support this sentence, but this is not accurate, The proper reference in 23.

Response: Proper reference has been added

6. Page 6, paragraph 2. The authors discuss the effects of GERD on the UES and its reflexes but do not review or reference all of the studies which have investigated the effects of esophageal acid exposure, a major constituent of GER, on the UES and its reflexes. Please review the effects of gastroesophageal reflux (GER) on the UES and its reflexes. This is basic to the purpose of this review.

Response: See additions below: “Studies regarding the role of pH of infusate in producing these reflexes have been contradictory. Several showing no difference in EUS pressure response between acidic and nonacidic infusate^{12,22,24} On the other hand, more recent studies in animal models suggest that pH plays a role in mediating response thresholds of these reflexes. Most notably, Lang et al.¹⁵ Found that short-term acute exposure of the thoracic esophagus to acid sensitized the EURR and desensitized the EUCR in decerebrate cats. A similar effect was seen after chronic acid exposure in awake, unanesthetized cats. I.e., compared to day 1, day 4 of acid exposure resulted in more attenuated EURR in response to air injection and dampened EUCR response. ¹⁵”

7. Page 8, paragraph 1. The authors suggest that there is an inability to distinguish between causal and effectual relationship of LPR with the sensitivity of EURR, but there are studies that have investigated the causal relationship. Please review and reference all appropriate studies that address this issue.

Response: See addition below: “The authors suggest this as a mechanism for a hypersensitive belch reflex contributing to regurgitation; however, they recognize the need to consider chronic inflammation from suprapharyngeal reflex as the cause of this impaired reflex.³⁸ However, prior animal studies would suggest that attenuated EUS relaxation is the cause of SERD symptoms rather than sequelae of inflammation.³⁹”

8. Summary, sentence 2; Th authors suggest that there is no evidence determining the effects of esophageal pH on the UES and its reflexes and this is false. This issue has been investigated and needs to be reviewed and referenced.

Response: See response to #6

Reviewer B

1. Line 112 - 114; the sentence "EUCR response to acidic and non-acidic liquid infusate, which has been replicated, most notably with subjects in the supine position." is unclear. Is there a difference in EUCR response between acidic and non-acidic liquid infusate? Please clarify.

Response: Additional paragraph added elaborating on relationship between EUS reflexes and pH above.

2. Line 178; I believe the word "milieu" may not be used correctly, although it is clear what the authors are trying to say. Would alter the word choice for the sake of clarity.

Response: Corrected

3. Line 183 - 185; how did Shaker et al artificially increase EUS pressure by 20-30 mmHg? Have any devices been developed, or are currently in development?

Response: See below “They augmented EUS pressure with a handmade upper esophageal sphincter assist device (UESAD) consisting of a cushion and elastic band which applied steady cricoid pressure.³⁷ “

4. Overall, this is a well written review on an understudied subject. It sheds light on the additional research that is required, while providing a good summary of what is known. Corrections are minor, and mostly serve to improve clarity of the manuscript. I would also recommend expanding on the therapeutic interventions aimed at the UES. What sort of devices have been proposed? Are there any medical interventions that augment UES tone?

Response: See below: “The Reflux Band™ by Somna therapeutics is the only FDA-approved, commercially available form of UESAD. ⁴²It is currently undergoing clinical trials looking at its potential role in reducing SERD symptoms in lung transplant patients. ⁴³”

Reviewer C

This is a short review about important problem for the diagnosis and therapeutic. Important publications were cited, however the revision is not complete. Some patients may have a permanent increase in UES pressure and a reduction of sphincter opening during swallowing. Although the manuscript has a partial vision of the problem it is important to know about the sphincter behavior during reflux and in patients with the disease. The diagnosis of supra esophageal reflux need a better method than we have nowadays.

Response: We would like to thank the reviewer for his comment. We agree with the comments. However, we are unclear as to exactly what he would like for us to add or delete.