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'This is the peer reviewed version of the following article: Fox M, Omari T, Rommel N. Supraesophageal Reflux Disease: Solving a Riddle Wrapped in a Mystery Inside an Enigma. *Gastroenterology*. 2015 Nov;149(6):1318-20.

which has been published in final form at

<http://dx.doi.org/10.1053/j.gastro.2015.09.033>

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Supra-Esophageal Reflux Disease: Solving a riddle wrapped in a mystery inside an enigma

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Symptoms referable to irritation and inflammation of the pharynx, larynx and bronchi are very common in the community. Hoarseness, persistent sore throat, globus and chronic cough are present in up to 25% of the primary care population and account for a large number of referrals to gastroenterologists, respiratory physicians and ear, nose and throat (ENT) specialists.¹ Epidemiological research has documented an association between gastro-esophageal reflux disease (GERD) and a range of “supra-esophageal” symptoms and diseases ([Table 1](#)). Further clinical studies report a high prevalence of typical reflux symptoms in patients with signs of laryngo-pharyngeal disease² and, also, a high frequency of throat and respiratory symptoms among patients with pathological esophageal acid exposure.³ Based on this evidence, the Montreal classification included so called laryngo-pharyngeal or supra-esophageal reflux disease (SERD) as a subcategory of GERD,⁴ and clinical reviews have proposed gastric acid and reflux suppression as empirical treatment for these “atypical” manifestations of GERD.⁵ Notwithstanding this broad based agreement, if reflux of gastric contents is a common cause of supra-esophageal symptoms and disease, then many issues remain unresolved. In many cases the mechanism of disease is a riddle. The inability of current investigations to establish an association between reflux events and symptoms is a mystery. The failure of proton pump inhibitors (PPI) to treat laryngo-pharyngeal symptoms or heal mucosal disease in well-designed clinical trials is an enigma. In this issue of *Gastroenterology*, Babaei and colleagues applied state-of-the-art physiological measurements to study the pharyngo-esophageal response to simulated reflux events.⁶ Their findings identified specific abnormalities in patients with symptoms suggestive of SERD. Moreover their approach to investigation could point the way to promising new clinical diagnostic tests for this condition.

Mechanism of disease

The simplest mechanism proposed for SERD is microaspiration of gastric contents into the pharynx and larynx.⁷ In vivo experiments suggest that minute amounts of acid are sufficient to cause mucosal damage, especially in the

presence of pepsin.⁸ However, in most cases, ambulatory pH-impedance monitoring detects very few pharyngeal reflux events and this *direct* mechanism alone cannot explain the frequent symptoms reported by many patients. Other proposals include the possibility that distal esophageal reflux causes laryngo-pharyngeal symptoms by an *indirect* mechanism either by triggering an antedromic vagovagal reflex and neurogenic inflammation, or by prompting repetitive swallowing behavior.⁷ An additional consideration is that acid exposure to the distal esophagus heightens visceral sensitivity of the whole organ through a central mechanism.⁹ If this effect extends to the larynx and pharynx, then this would lower the sensory threshold not only to further reflux events but also to a range of other potential stimuli such as temperature change, cigarette smoke, airborne allergens and ingestion of alcohol or other irritants.⁷

Physiological Measurement

In patients with heartburn, acid regurgitation and reflux esophagitis the cause of laryngo-pharyngeal symptoms and disease may be obvious. However, the majority of patients with suspected SERD do not have typical reflux symptoms or mucosal disease.¹⁰ In this group, physiological measurements that detect reflux events at, or close to, the site of pathology provide objective evidence to support of the diagnosis. Studies that include pharyngeal pH sensors in addition to esophageal sensors may be more discriminatory of SERD patients.¹¹ The current standard is ambulatory pH-impedance reflux monitoring.¹² This technology can detect both acid and non-acid reflux and, in principle, establish a causal association between these events and symptoms. Unfortunately, there is little consensus regarding the optimal acquisition, analysis or interpretation of this data. Moreover, in practice, if isolated pharyngeal reflux events are sufficient to cause disease, if symptoms are present all the time, or if there is only an indirect link between reflux and symptoms, then even the most accurate ambulatory reflux monitoring will not establish a definitive SERD diagnosis. These issues are compounded by the fact that symptoms such as hoarseness and chronic cough are very common and have multiple potential causes that may coexist with

GERD by chance. These are real and important concerns because treatment decisions, including referral for anti-reflux surgery, are based on this information.

Given the limitations of existing tests, new methods to detect SERD are of interest. Measurement of pepsin and bile acids in the saliva have been proposed as an 'office-based' method for detecting reflux. Recent studies indicate that high levels of pepsin provide a specific marker of GERD.¹³ The presence of this gastric enzyme in the throat can be explained only by supra-esophageal reflux and, therefore, this approach may be particularly value for SERD diagnosis.¹⁴ The same concept can be applied by nuclear imaging. Scintigraphy is used to detect reflux to the pharynx after ingestion of a radio-labelled drink, with late studies of the lungs obtained to detect aspiration.¹⁵ Both these investigations are well-tolerated and require less expertise to interpret than pH-impedance studies; however, neither provides insight into the mechanism of disease.

To address this issue, the current study applied high-resolution impedance manometry (HRiM) to obtain a detailed description of sensory-motor mechanisms that control upper esophageal sphincter (UES) function and how this is disrupted in patients with typical symptoms of GERD and SERD.⁶ It is known from the previous work by Reza Shaker's group,¹⁶ that both relaxation and contractile UES responses are present in health, each governed by independent neural circuits that are activated in relation to the rate, magnitude and physical properties of distending stimuli. Relaxation enables venting of gas ("belching"). Contraction guards against reflux of gastric contents into the pharynx. The authors identified the UES relaxation reflex (RR) and contraction reflex (CR) by HRM and SER events using impedance data. These observations revealed that some patients with SERD symptoms have aberrant UES responses to rapid esophageal infusion of liquid (i.e. simulated reflux) that were not seen in patients with GERD symptoms or healthy controls. Specifically, rather than an effective contraction of the UES and proximal esophagus to clear "refluxate" away from the sensitive laryngo-pharyngeal region, some patients had an inappropriate

UESRR and / or ineffective UES and esophageal CR during liquid reflux. The absolute frequency of SER during individual studies and how often SER was associated with each form of dysfunction was not reported and therefore the overall extent to which these aberrant responses are permissive of reflux is unknown; nevertheless, the unique abnormality in patients with SERD symptoms were inappropriate UESRRs. Although failure to initiate UES and esophageal CR also occurred in this group, the latter abnormality was seen also in GERD, and SER was never reported following “isolated” failure of the protective response.

This study provides new insight into the pathophysiology of SERD. The presence of inappropriate UESRR in patients with laryngo-pharyngeal symptoms is consistent with microaspiration as a mechanism of disease. In addition, the technology and methodology used by this group is of interest to clinicians looking for a new, more informative diagnostic test for SERD. HRiM provides a comprehensive, non-radiological assessment of pharyngo-esophageal function. High resolution manometry with spatiotemporal “Clouse” plots delivers a continuous representation of motor activity from the pharynx to the stomach. Intraluminal impedance detects bolus movement by measuring changes in resistance between multiple pairs of electrodes. To date, this combined technology has been applied most often to study patients with pharyngeal swallowing problems and to assess the risk of aspiration.¹⁷ The findings reported here suggest that HRiM could be applied also to assess the risk of supra-esophageal reflux in patients with laryngo-pharyngeal symptoms. Importantly, the HRiM methodology is different to ambulatory pH-impedance monitoring or stationary observations after a test meal because, rather than relying on the detection of spontaneous SER events, a standardized challenge designed to simulate gastro-esophageal reflux (i.e. esophageal infusion) is applied to identify patients at risk of SERD.

Further validation is required before HRiM could be used for SERD diagnosis. Surprisingly, the current study did not apply standardized questionnaires,

laryngoscopic assessment or physiological studies to define study groups. Not one of these investigations represents a “gold standard”; however, symptoms are non-specific and the differential diagnosis for patients with “troublesome regurgitation along with at least one supra-esophageal manifestation” (the entry criterion used in the study) includes motility disorders, rumination syndrome and a number of ENT or respiratory diseases.¹⁸ This could explain why only 5/19 patients with “typical” SERD symptoms had the “characteristic” UESRR abnormality after rapid esophageal saline infusion. Future studies should apply standardized inclusion criteria with either pathological acid exposure or a positive reflux-symptom association on pH-impedance monitoring. Additionally, HRiM data analysis could be optimized. In this paper assessment of impedance was subjective and considered separately to the pressure measurements. Pressure Flow Analysis (PFA) is a semi-automated method which integrates high resolution pressure and impedance signals to obtain objective metrics that cannot be determined by either method alone.¹⁹ Application of PFA in patients with pharyngeal dysfunction identifies biomechanical factors that determine the success or failure of the swallow and defines the risk of aspiration.^{19, 20} This includes not only UES relaxation, but also UES opening and the efficacy of pharyngeal clearance.²⁰ Adapting this approach, UES responses to esophageal infusion could be quantified in terms of “flow permissive characteristics” to detect factors that determine the risk of supra-esophageal reflux.

The success of scientific medicine is based on the identification and treatment of the pathophysiological basis of disease. To date, the diagnosis of SERD has been based as much on subjective assessment as objective physiology. Now, as with the introduction of HRM and the Chicago Classification of esophageal motility disorders a few years ago, new technology and methods is driving progress in the pharyngo-esophageal region. HRiM combined with analysis that utilizes all the information acquired, are now available to describe the causes of SERD, identify individual patients that can benefit from anti-reflux treatment and, in the process, solve this riddle wrapped in a mystery inside an enigma.

Table 1

<u>Extraesophageal conditions linked to SERD</u>	
Symptoms	Diseases
• Acid Regurgitation	▪ Dental erosions
• Voice change	▪ Sinusitis
• Hoarseness	▪ Posterior Laryngitis
• Chronic sore throat	▪ Vocal cord ulceration
• Repetitive throat clearing	▪ Laryngeal polyps
• Globus sensation	▪ Cancer of pharynx / larynx
• Chronic cough	▪ Bronchiectasis
• Recurrent aspiration	▪ Non-atopic asthma

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