Coughing our guts up: how do we diagnose reflux cough?

Mengru Zhang and Dominic L. Sykes

Respiratory Research Group, Hull York Medical School, Hull, UK.

Corresponding author: Dominic Sykes (dominic.sykes2@nhs.net)

Shareable abstract (@ERSpublications)
Should Peptest be routinely used in a cough clinic? The answer is yes, but only as part of more intricate workup in which discovering the nature of the reflux is as important as identifying its presence. https://bit.ly/3QkbChb

Cite this article as: Zhang M, Sykes DL. Coughing our guts up: how do we diagnose reflux cough?. *ERJ Open Res* 2024; 10: 00406-2024 [DOI: 10.1183/23120541.00406-2024].

Received: 18 April 2024
Accepted: 18 April 2024

The phenomenon of chronic cough has long been classified by its suggested aetiology. Indeed, one of the pioneers of disease classification Dr Thomas Sydenham, a 17th Century English physician most famous for his description of Sydenham Chorea or St Vitus' dance, described a multitude of phenotypes of chronic cough in his 1668 essay "*Tussis*" [1]. One phenotype that he entitled tussis *callida per accidens* describes those who experience it to be "*of more sanguine and robust constitutions…who drink strong liquors*" and warns that in such patients "*any strong wines or vinous spirits should be avoided*". To anyone who has enjoyed a glass or two of a particularly rich red wine, it may be deduced that Sydenham was describing the cough which accompanies gastro-oesophageal reflux, also known as gastro-oesophageal reflux cough (GORC).

In this fascinating treatise, Sydenham goes on to describe that in these patients their phlegm "*bakes up sooner and stuffs the passages of the lungs, from which and great inflammation upon all the spirituall parts of the cough is made*". While this may not be wholly accurate, it is not a million miles away from our current understanding of GORC some 356 years later.

Chronic cough is still acknowledged as a heterogeneous disease with a diverse set of potential causes, and reflux is considered one of the primary contributing factors [2]. In this issue of *ERJ Open Research*, Gu *et al*. [3] reported on the value of Peptest (RD Biomed, Hull, UK), which measures salivary pepsin concentration, in identifying GORC. They found that the salivary pepsin demonstrated comparable diagnostic value to the GerdQ questionnaire in diagnosing an acid-reflux cough and superior value in diagnosing a non-acid reflux cough. This is a rather expected result as this questionnaire is no more effective than flipping a coin in predicting non-acid reflux [4], probably due to the fact it primarily focuses on typical manifestations of acid reflux which are rarely seen in non-acid reflux [5], and therefore its utility in the cough clinic is questionable.

The Peptest is a marketed diagnostic tool and is the first appropriate noninvasive objective measurement to diagnose reflux by detecting the presence of pepsin in saliva samples, which can be used as a surrogate biomarker for gastro-oesophageal reflux [6]. Thus, it may effectively reveal the true issue affecting these individuals. A salivary pepsin concentration of 76 $ng \cdot mL^{-1}$ has been reported to diagnose gastro-oesophageal reflux disease with a sensitivity of 73% and a specificity of 88.3% [7]. Gu *et al*. [3] reported a similar diagnostic value of salivary pepsin in GORC with a sensitivity of 83.6%, a specificity of 82.7% and a cut-off value of 76.10 $ng \cdot mL^{-1}$. Notably, in this study, saliva samples were taken in the morning when patients were fasting. Usually, when rising from bed in the morning, the air trapped in the stomach during sleep travels up the gastrointestinal tract [8]. This is more evident in coughs induced by non-acid reflux, which is also called airway reflux or silent reflux. In this condition the gaseous refluxate is believed to be microaspirated which may be one of the aetiological agents resulting in non-acid reflux induced cough hypersensitivity [9]. This microaspiration has been visualised in patients with laryngopharyngeal reflux using a modified reflux scintigraphy technique reported by Park *et al*. [10].

Gu *et al*. [3] reported the comparable value of salivary pepsin in predicting acid and non-acid reflux induced cough. This indicates that Peptest is useful in diagnosing reflux-associated cough but cannot differentiate between acid and non-acid reflux cough, which the authors duly acknowledge in their discussion. Therefore, with Peptest, we are left with a biomarker that can be used to identify reflux, but does not elucidate the nature of the reflux. The question remains, how can we be certain of the aetiology of the cough and how do we treat such patients?

If we allow ourselves to think simplistically, reflux cough may be dichotomised into acid-reflux induced cough (GORC) and non-acid gaseous reflux induced cough (airways reflux). Both disease processes have plausible mechanisms leading to the development of chronic cough. One of the primary theories of development of GORC is that the cough may be directly initiated from oesophageal irritation by acid and non-acid refluxate, which led to the concept of the "oesophago–bronchial reflex" [11]. This concept suggests a crosstalk at the nucleus tractus solitarius (nTS) between the stimuli from oesophageal and airway neurons converging in this area, it is thought acid-mediated irritation of the oesophagus engenders a "referred" initiation of the cough reflex. Animal studies have evidenced this model [12]. Airway reflux, however, is primarily attributed to oesophageal dysmotility. In those who failed to respond to the aetiology-oriented therapy, which is usually a significant proportion of patients (hence the term refractory chronic cough), high-resolution oesophageal manometry (HROM) revealed that oesophageal dysmotility was present in over two-thirds of patients [13]. Furthermore, only around a third of patients in this study returned a positive DeMeester score, indicating classical acid reflux. Oesophageal motility disorders, in conjunction with oesophageal vagal hypersensitivity, can lead to prolonged transient relaxation of the lower oesophageal sphincter and impaired oesophageal clearance. This, in turn, allows for regurgitant upward aspiration, irritating the airways that share vagal nerve innervation with the oesophagus [14]. This disease process can be identified by a validated diagnostic questionnaire, the Hull Airway Reflux Questionnaire (HARQ), with an upper limit of normal of 14. Global patients with a rigorous diagnosis of chronic cough in the phase III clinical trial of gefapixant scored an average of 40 out of 70 [15], and over 90% scored over 14 in a study with a sample size of 2397 chronic cough patients [16]. Moreover, in the aforementioned study the degree of oesophageal dysmotility was positively correlated with the HARQ score.

Peptest may have limitations in identifying airway reflux as it cannot differentiate between acid and non-acid reflux. However, a positive Peptest result coupled with a clinically significant HARQ score indicates the diagnosis of non-acid reflux cough. HROM combined 24-hour pH monitoring may also be helpful to confirm the motility of oesophagus and the nature of the reflux. Once airway reflux is identified, pro-motility medications, such as baclofen, metoclopramide, azithromycin and octreotide, should be considered. Proton-pump inhibitors (PPIs), despite being widely used to treat reflux-related conditions, have limited effectiveness in managing airway reflux as they only block acid secretion rather than inhibit reflux itself [17, 18]. The latest cough guidelines from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) do not recommend PPIs as the sole treatment for reflux cough unless there is clear evidence of abnormal acid reflux [19, 20].

Clearly the treatment of cough has developed significantly since Sydenham's day and despite "The English Hippocrates" describing his prescription of "*oyl of sweet almonds*" as "*beyond all comparison the best… it being a well concocted medecin*" it does not currently make it into the ERS or ATS guidelines! However, one may argue that despite our advances, we are still confronted with an extremely prevalent disease in which no consensus on investigation or management strategy exists.

Integrating Peptest into the diagnostic algorithm may enhance diagnostic accuracy and enable targeted treatment strategies tailored to the underlying cause, thereby reducing unnecessary use of medications. It is important to consider the timing of saliva sampling for Peptest, either after cough attacks or in the morning and after meals, as coughing is often an episodic phenomenon with a temporal pattern. So, should Peptest be routinely tested in a cough clinic? The answer is yes, but only as part of a more intricate workup in which the discovering the nature of the reflux is as important as identifying its presence.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: All authors have nothing to disclose.

References

1 Hill C. Dr. Thomas Sydenham (1624–1689): his life and original writings. *Med Hist* 1967; 11: 206–207.

2 Kahrilas PJ. Chronic cough and gastroesophageal reflux disease: new twists to the riddle. *Gastroenterology* 2010; 139: 716–718.
3 Gu W, Chen W, Zhang T, *et al.* Diagnostic value of the pepsin concentration in saliva and induced sputum for gastroesophageal reflux-induced chronic cough: a prospective clinical study. *ERJ Open Res* 2024; 10: 00046-2024.
4 Xu X, Chen Q, Liang S, *et al.* Comparison of gastroesophageal reflux disease questionnaire and multichannel intraluminal impedance pH monitoring in identifying patients with chronic cough responsive to antireflux therapy. *Chest* 2014; 145: 1264–1270.
5 Xu X, Yang Z, Chen Q, *et al.* Comparison of clinical characteristics of chronic cough due to non-acid and acid gastroesophageal reflux. *Clin Respir J* 2015; 9: 196–202.
6 Race C, Chowdry J, Russell JM, *et al.* Studies of salivary pepsin in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2019; 49: 1173–1180.
7 Du X, Wang F, Hu Z, *et al.* The diagnostic value of pepsin detection in saliva for gastro-esophageal reflux disease: a preliminary study from China. *BMC Gastroenterol* 2017; 17: 107.
8 Zhang M, Sykes DL, Brindle K, *et al.* Chronic cough–the limitation and advances in assessment techniques. *J Thorac Dis* 2022; 14: 5097–5119.
9 Morice AH. Airway reflux as a cause of respiratory disease. *Breathe* 2013; 9: 256–266.
10 Park JS, Burton L, Van der Wall H, *et al.* Modified reflux scintigraphy detects pulmonary microaspiration in severe gastro-esophageal and laryngopharyngeal reflux disease. *Lung* 2021; 199: 139–145.
11 Smith JA, Houghton LA. The oesophagus and cough: laryngo-pharyngeal reflux, microaspiration and vagal reflexes. *Cough* 2013; 9: 1.
12 Canning BJ, Mori N. An essential component to brainstem cough gating identified in anesthetized guinea pigs. *FASEB J* 2010; 24: 3916–3926.
13 Sykes DL, Crooks MG, Hart SP, *et al.* Investigating the diagnostic utility of high-resolution oesophageal manometry in patients with refractory respiratory symptoms. *Respir Med* 2022; 202: 106985.
14 Houghton LA, Lee AS, Badri H, *et al.* Respiratory disease and the oesophagus: reflux, reflexes and microaspiration. *Nat Rev Gastroenterol Hepatol* 2016; 13: 445–460.
15 McGarvey LP, Birring SS, Morice AH, *et al.* Efficacy and safety of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet* 2022; 399: 909–923.
16 van den Berg JWK, Baxter CA, Edens MA, *et al.* The demographics, clinical characteristics and quality of life of patients with chronic cough from the Isala Cough Clinic in the Netherlands. *ERJ Open Res* 2022; 8: 00232-2022.
17 Faruqi S, Molyneux I, Fathi H, *et al.* Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study. *Respirology* 2011; 16: 1150–1156.
18 Blake K, Teague WG. Gastroesophageal reflux disease and childhood asthma. *Curr Opin Pulm Med* 2013; 19: 24–29.
19 Kahrilas PJ, Altman KW, Chang AB, *et al.* Chronic cough due to gastroesophageal reflux in adults: CHEST guideline and expert panel report. *Chest* 2016; 150: 1341–1360.
20 Morice AH, Millqvist E, Bieksiene K, *et al.* ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020; 55: 1901136.