Gastro-oesophageal reflux-related chronic cough: can new tools improve patient assessment?

Shuxin Zhong [1], Ruchong Chen [1,2] and Huda Badri [3,4]

[1]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, National Center for Respiratory Medicine, Department of Allergy and Clinical Immunology, Joint International Research Laboratory of Respiratory Health, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China. [2]Guangzhou National Laboratory, Guangzhou, China. [3]School of Biological Sciences, Faculty of Biology, Medicine and Health Sciences, University of Manchester, Manchester, UK. [4]North Manchester General Hospital, Manchester University NHS Foundation Trust, Manchester, UK.

Corresponding author: Huda Badri (huda.badri@postgrad.manchester.ac.uk)

Shareable abstract (@ERSpublications)
Novel impedance pH monitoring parameters, such as mean nocturnal baseline impedance and post-reflux swallow induced peristaltic wave index, may be better markers for assessing chronic cough related to oesophageal hypersensitivity https://bit.ly/41woxTD

Cite this article as: Zhong S, Chen R, Badri H. Gastro-oesophageal reflux-related chronic cough: can new tools improve patient assessment? *ERJ Open Res* 2025; 11: 00794-2024 [DOI: 10.1183/23120541.00794-2024].

Received: 7 Aug 2024
Accepted: 24 Nov 2024

Gastro-oesophageal reflux (GOR) is often cited as an important cause of chronic cough (persistent cough of >8 weeks' duration) [1]. The physical proximity of the oesophagus to the bronchial tree and the shared embryonic origin of their neuronal supply form the basis of several suggested mechanisms for GOR-related cough [2]. These include micro-aspiration of refluxate, laryngopharyngeal reflux (LPR) causing upper airway hypersensitivity and reflux contained within the oesophagus causing oesophageal–bronchial neuronal cross talk [2]. However, the response of cough to reflux therapy, whether proton pump inhibitors (PPIs), H2 antagonists and/or reflux surgery, has been disappointing. So much so that current refractory cough guidelines only recommend PPI trials in patients who also present with typical GOR symptoms, such as heartburn [3, 4]. Indeed, even in patients with typical reflux ∼50% do not respond to PPI therapy [5]. The likelihood of success of PPI therapy in treating cough increases by two-fold in the presence of typical GOR symptoms [6]. There is also data to suggest that in patients who are seemingly nonresponsive to PPIs, more prolonged/intensive treatment courses may subsequently result in a response [7]; thus, suggesting that in a carefully selected cohort of patients the response to these treatments may be higher. Objective reflux-cough assessment tools may enable better identification of PPI-responsive patients, limiting excessive use of PPI therapy as well as shedding light on the mechanisms underlying GOR-related cough.

Impedance pH monitoring studies are established reflux assessment techniques and enable the measurement of parameters such as acid exposure time (AET), measurement of oesophageal junction function, symptom association probability (SAP) and symptom index (SI). The use of these parameters has been extrapolated to reflux-cough symptoms. A raised AET and positive SAP in patients with typical reflux symptoms and cough reliably confirms a diagnosis of GOR-related chronic cough. However, these measures have several limitations. The AET (defined as percentage of time with pH <4.0) is a measure of acid exposure and thus does not consider weakly acidic or non-acid reflux. Several studies have suggested that cough can be evoked with physiological levels of reflux [8]. The SAP and SI are used to determine the likelihood of a patient's symptoms being related to reflux and thus are superior to AET as temporal relationships can be established. However, SAP and SI are also dependent on the acidity of reflux events and thus may not be accurate enough for non-acid/weakly acidic events [9]. Furthermore, they are entirely dependent on accurate associated event capture. In clinical practice and most research studies, GOR symptom diaries and push button recorders are used to capture patient-reported events. This is problematic, as a high level of compliance is needed and symptoms are often subjective. These tools are even more unreliable in the context of chronic cough as these patients often have multiple bouts of coughing which

will be missed without objective, concurrent cough monitoring. Furthermore, neither the AET nor the SAP/SI account for reflux volume. This limits the usefulness of the SAP and SI parameters in evaluating the association between reflux and cough. In addition, it is not uncommon in clinical practice to see patients with GOR symptoms and chronic cough and a positive SAP and SI, but a normal AET and reflux frequency, which makes diagnosis challenging. One of the difficulties of studying the impact/effect of GOR on the pathophysiology of chronic cough is the lack of accurate, validated tools for assessing reflux–cough associations. This is especially true in the measurement of proximal reflux.

In this issue of *ERJ Open Research*, Li *et al.* [10] evaluate the role of two novel impedance-pH monitoring parameters: mean nocturnal baseline impedance (MNBI) and post-reflux swallow induced peristaltic wave index (PSPWI) in GOR-related cough.

The MNBI correlates inversely with AET and is a marker for abnormal mucosal integrity [11]. The PSPWI offers better assessment of clearance of refluxate [11]. Both parameters have been suggested as better markers of oesophageal hypersensitivity [11]. Furthermore, MNBI and PSPWI have been shown to improved diagnostic accuracy of pH impedance for GOR, especially when combined with AET [12]. Recent studies have demonstrated significantly lower MNBI and PSPWI values in those with GOR compared to healthy volunteers [13]. MNBI and PSPWI may differentiate non-erosive reflux disease (NERD) from functional heartburn, and correlate with PPI treatment efficacy in patients with NERD [14]. PSPWI and MNBI are independently related to PPI-responsive heartburn symptoms [15]. Of note, lower distal MNBI has been observed in PPI-responders with GOR [7, 14].

Li *et al.* [10] hypothesise that PSPWI and MNBI could serve as independent predictors of PPI-refractory, GOR-related chronic cough. Their study shows lower PSPWI and proximal MNBI ($\leqslant$39.90% and $\leqslant$2233.58 Ω, respectively) in GOR-related cough patients in keeping with published, typical GOR data. No significant differences were found in distal MNBI between the two groups, while proximal MNBI was lower in the PPI-refractory group. Interestingly, Li *et al.* [10] found that PSPWI and MNBI had moderate sensitivity and specificity in identifying poor response of cough to PPIs.

The authors' findings offer novel insights into assisting clinicians in early identification of PPI-refractory cough patients [10]. Their findings suggest that GOR-related cough may be associated with impaired proximal oesophageal mucosal integrity and/or prolonged exposure of the oesophageal mucosa to acidic and weakly acidic refluxates. Thus, increasing the risk of upper airway hypersensitivity. These findings give additional weight to the oesophageal–bronchial cough reflex and neurogenic inflammation theory, rather than micro-aspiration, as the primary mechanism of GOR-related cough [2, 16].

MNBI and PSPWI may also provide a solution to "on treatment" reflux studies. Ideally, objective GOR assessments should be made "off treatment". However, in some patients this is not possible due to their GOR symptom burden. Compared with AET, MNBI and PSPWI may be less affected during treatment with PPIs, and thus provide a more comprehensive assessment of oesophageal function.

There are, however, barriers to their use. PSPWI calculation requires a laborious manual review of each patient's tracing to ensure each reflux and post-reflux swallow wave meet the required criteria. This is not possible in the setting of most clinical services and opens the measure to the introduction of confirmation bias. All reflux-cough evaluation parameters, including MNBI and PSPWI, require invasive pH impedance studies. Many patients find these uncomfortable and they are not a widely available resource. In clinical practice, limited trials of PPIs in patients with typical reflux symptoms and cough are still the first-line approach. Progression to pH impedance studies should be limited to those with ongoing reflux symptoms who have not responded to treatments as per current GOR and refractory chronic cough guidance.

The strength of the study lies in the well characterised cohort of patients and strong study design with significant effort to treat all components of GOR. Unfortunately, Li *et al.* [10] did not use acoustic cough recording for their SAP/SI calculations, which significantly reduces the reliability of these measurements in cough.

Will MNBI and PSPWI significantly alter GOR-related cough management? Probably not. They do, however, show promise as novel end-points in studies evaluating the relationship between GOR and cough.

We need to consider how to use indices obtained from oesophageal manometry and pH impedance testing, other than MNBI and PSWI, in future studies. For example, measures of ineffective oesophageal motility such as distal contractile integral, distal latency, peristaltic breaks and failed peristalsis. Further studies are

required to clarify the association between oesophageal hypersensitivity and chronic cough, and to better understand the complex pathophysiology of GOR-related cough.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: S. Zhong has nothing to disclose. R. Chen is an Associate Editor of this journal; and has received research funding from AstraZeneca and GlaxoSmithKline, and honoraria for lectures, presentations or speaker bureaus from AstraZeneca, GlaxoSmithKline, Novartis and Sanofi, outside the submitted work. H. Badri receives research funding from the North West Lung Charity, Manchester UK and the National Institute for Health and Care Research (NIHR) UK.

References

1 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.
2 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.
3 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.
4 Parker SM, Smith JA, Birring SS, *et al.* British Thoracic Society Clinical Statement on chronic cough in adults. *Thorax* 2023; 78: Suppl. 6, s3–s19.
5 Delshad SD, Almario CV, Chey WD, *et al.* Prevalence of gastroesophageal reflux disease and proton pump inhibitor-refractory symptoms. *Gastroenterology* 2020; 158: 1250–1261.
6 Badri H, Satia I, Bansal V, *et al.* Heartburn as a marker of the success of acid suppression therapy in chronic cough. *Lung* 2021; 199: 597–602.
7 Ribolsi M, Savarino E, Rogers B, *et al.* High-resolution manometry determinants of refractoriness of reflux symptoms to proton pump inhibitor therapy. *J Neurogastroenterol Motil* 2020; 26: 447–454.
8 Smith JA, Decalmer S, Kelsall A, *et al.* Acoustic cough-reflux associations in chronic cough: potential triggers and mechanisms. *Gastroenterology* 2010; 139: 754–762.
9 Slaughter JC, Goutte M, Rymer JA, *et al.* Caution about overinterpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2011; 9: 868–874.
10 Li W, Sha B, Bai H, *et al.* How to distinguish PPI-refractory from PPI-responsive patients in gastro-oesophageal reflux-induced chronic cough: post-reflux swallow induced peristaltic wave index and mean nocturnal baseline impedance provide new predictive factors. *ERJ Open Res* 2024; 10: 00299-2024.
11 Gyawali CP, Kahrilas PJ, Savarino E, *et al.* Modern diagnosis of GERD: the Lyon Consensus. *Gut* 2018; 67: 1351–1362.
12 Sha B, Li W, Bai H, *et al.* How to diagnose GERC more effectively: reflections on post-reflux swallow-induced peristaltic wave index and mean nocturnal baseline impedance. *BMC Pulm Med* 2024; 24: 269.
13 Farré R, Blondeau K, Clement D, *et al.* Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. *Gut* 2011; 60: 885–892.
14 Wang Y, Ye B, Wang M, *et al.* Esophageal nocturnal baseline impedance and post-reflux swallow-induced peristaltic wave index in identifying proton pump inhibitor-refractory non-erosive reflux disease. *J Neurogastroenterol Motil* 2021; 27: 525–532.
15 Frazzoni L, Frazzoni M, de Bortoli N, *et al.* Postreflux swallow-induced peristaltic wave index and nocturnal baseline impedance can link PPI-responsive heartburn to reflux better than acid exposure time. *Neurogastroenterol Motil* 2017; 29: e13116.
16 Zhi H, Zhong M, Huang J, *et al.* Gabapentin alleviated the cough hypersensitivity and neurogenic inflammation in a guinea pig model with repeated intra-esophageal acid perfusion. *Eur J Pharmacol* 2023; 959: 176078.