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## GASTRO-OESOPHAGEAL REFLUX EVENTS: JUST ANOTHER TRIGGER IN CHRONIC COUGH?

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Gastroesophageal reflux disease (GORD) is considered a common cause of chronic cough, either alone or in association with nasal disease and/or asthma(1). This along with the fact that there are currently no specific therapies approved for the treatment of chronic cough, has led to extensive use of acid suppressants, such that one U.S. study in patients with extra-oesophageal manifestations of GORD, of which 50% had cough, estimated costs to be 4-5 times those associated with their use in typical GORD(2). Despite this widespread use, a significant proportion of patients with chronic cough thought to be due to GORD remain refractory to acid suppression. Indeed, multiple studies and meta-analyses have failed to document a therapeutic benefit of acid suppression in chronic cough(3).

A growing number of studies suggest that in 30-48% of patients, coughing episodes seem to be temporally linked to reflux events, irrespective of their acidity or the presence of other conditions contributing to coughing(1,4,5). Notably, patients exhibiting such associations, i.e. a positive symptom association probability (SAP) for cough preceded by reflux ( $SAP_{R-C}$ ), appear to have no more erosive disease or oesophageal exposure to reflux, with little reaching the proximal oesophagus, than those with a negative  $SAP_{R-C}$ (5).  $SAP_{R-C}$  positive patients however, do have a heightened cough response to inhaled citric acid compared with  $SAP_{R-C}$  negative patients, suggesting a neuronal sensitization process maybe linking reflux events to cough(5).

The study by Herregods and colleagues (6) in the current issue of *Gut* aimed to extend these observations by investigating whether characteristics other than the acidity of refluxate may be important in triggering cough. To do this they compared the characteristics of reflux events that appeared to precede cough with those that did not, in cough patients identified with a positive  $SAP_{R-C}$  and in whom other causes of cough had been excluded. Along with confirming that the acidity of refluxate is unlikely to play a key role (1,4,5), they also reported that the nadir pH, the magnitude of the pH drop, acid clearance time, and acid burden times longer than 15 minutes before the initiation of cough did not differ between reflux episodes that were associated with cough and those that were not. They did report that the volume and the duration of exposure of the oesophagus to refluxate prior to cough, which appeared to be influenced by its proximal extent, seemed to be important for reflux to induce cough. At group level however, the number of reflux events reaching the proximal oesophagus [8(3-15); median(IQR)] was similar to that reported by Smith *et al* (5) [9(5-19)], and no different from controls (7). Moreover, only approximately 20% of the reflux episodes (whether proximal or distal) were followed by coughing, suggesting that even in  $SAP_{R-C}$  positive patients, most coughs are triggered by alternative processes.

However, the results of this study must be interpreted cautiously as oesophageal manometry was used to identify coughing. Although this technique seems to be superior to relying upon patients pushing an event button on the impedance recorder to register coughs(1,4), manometry has not been validated for 24h ambulatory cough detection. Only cough 'bursts' (also known as epochs/peals) are quantified manometrically; single coughs cannot be discriminated from throat

clearing or other pressure artefacts, so they are ignored. In our experience of acoustic monitoring, the pattern of coughing typically consists of long epochs in chronic cough patients and single cough events are uncommon. Therefore it is not clear why this technique seems to under report cough bursts by about 50% compared with the number of cough epochs identified from acoustic recordings, which are generally considered the gold standard. The incomplete detection of cough events does have implications for the study findings, including potential underestimation of the percentage of patients identified with a positive  $SAP_{R-C}$ . More importantly, it must be acknowledged that the features of the reflux events found to be associated with bursts of manometrically detected cough in this study, may not be representative of all reflux events associated with coughing when more sensitive cough detection methods are used.

Given these difficulties, it is reassuring that the authors did confirm previous findings that the acidity of refluxate is unlikely to be a key factor in whether reflux triggers coughing. Moreover the average numbers of reflux events and proportion reaching the proximal oesophagus were within normal limits, consistent with the concept that in such patients coughing is triggered by physiological levels of oesophageal reflux. Indeed although the volume clearance times of the reflux events associated with cough bursts were longer than those not associated, neither would be considered abnormal for patients in this age range(7).

Pharmacological intervention studies are providing additional insights into the mechanisms at play in chronic cough patients. Therapeutics modifying neuronal function such as low dose morphine(8) and gabapentin(9) have already been shown to improve cough specific quality of life. Most interestingly, a P2X3 receptor antagonist has exhibited the greatest efficacy, reducing acoustically recorded daytime cough frequency by 75% over placebo(10). Together with the difficulties in demonstrating efficacy for proton pump inhibitors in similar patients, the weight of current evidence favours the notion that neuronal dysfunction lies at the root of chronic coughing. While reflux-cough associations are most readily explained by dysfunction of central neuronal pathways, the P2X3 antagonist tested (AF-219/MK-7264) poorly penetrates the central nervous system, providing compelling evidence that peripheral neuronal activity is also important. Hence, there is still much to be elucidated about the specific neuronal mechanisms underlying chronic cough. Nonetheless, we suggest that analogous to the tendency for these patients to cough when their airway vagal afferents are exposed to environmental irritants, many chronic patients respond in the same manner when their oesophageal vagal afferents are exposed to reflux events. Consistent with this hypothesis, reflux events of greater volume, longer duration, or involving the full length of the oesophagus might be expected to provide the greatest stimulus to oesophageal vagal afferents and therefore be more likely to evoke multiple coughs.

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**Contributors** JAS and LAH contributed equally to the writing of this manuscript

**Competing interests** JAS is a named inventor on a patent, owned by University Hospital of South Manchester, describing a method for cough detection and monitoring licensed to Vitalograph; however, no financial benefits have been received. Afferent Pharmaceuticals paid staff cost for conduct of study (ref 10) to the University Hospital of South Manchester and University of Manchester.

**Competing interests** Commissioned; internally peer reviewed

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