Gastro-oesophageal Reflux and Cough
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Abstract
Gastro-oesophageal reflux, either singly or in association with postnasal drip and/or asthma is considered to be a cause of chronic cough. The amount and nature of gastro-oesophageal reflux however is often normal with acid suppression having very little, if any therapeutic effect in these patients. This review examines the challenges posed when exploring the reflux-cough link, and discusses the merits and limitations of the proposed mechanisms of reflux leading to cough.

Introduction
Chronic cough is a debilitating condition that significantly affects the quality of life of its sufferers.1,2 Cough-variant asthma, postnasal drip and gastro-oesophageal reflux disease (GORD) either singly or in association, are thought to be responsible for chronic cough in the majority of non-smoking patients who are not taking ACE inhibitors and have a normal chest x-ray.3 GORD has been proposed to be associated with cough in up to one third of patients.4 Evidence supporting this comes from studies measuring reflux (ambulatory oesophageal pH monitoring, combined impedance/pH monitoring) and its temporal association with cough,5-9 and studies assessing the pH monitoring, combined impedance/pH monitoring) and its temporal association with cough,5-9 and studies assessing the patient’s response to medical10 and surgical treatment.11 This review summarises the possible mechanisms whereby gastro-oesophageal reflux may be associated with chronic cough.

Mechanisms of Reflux-associated Chronic Cough
There are three proposed mechanisms of reflux-associated chronic cough: Laryngopharyngeal reflux (LPR), microaspiration, and oesophageal-bronchial reflex (Figure 1).

Laryngopharyngeal reflux (LPR)
LPR is a term first used by Ear Nose and Throat specialists12 to describe episodes of liquid and/or gaseous stomach contents, including acid and pepsin, passing through the Upper Oesophageal Sphincter (UOS) and reaching the larynx and pharynx. LPR is thought to be responsible for laryngeal irritation and also inflammation which then give rise to a variety of symptoms such as cough, throat clearing, and voice changes.13 Assessment of LPR however is difficult and often relies upon tools such as the Reflux Symptom Index (RSI)14 and Reflux Finding Score (RFS),15 despite neither symptoms16 nor laryngoscopy findings17 being specific for LPR.

Others have made attempts to measure reflux events in the larynx and pharynx using impedance18,19 and/or pharyngeal pH20,21 but the data obtained using these techniques have often been inconsistent20,21 even in healthy controls.21 Indeed, a recent study reported that the measurement of reflux in the pharynx using impedance is extremely challenging given the instability of baseline measures due to air in pharynx and the difficulties in discriminating pharyngeal reflux from swallowing.21 Likewise new oropharyngeal pH only measures (Restech) which allow measurement of pH changes due to aerosolised reflux, may also be confounded by pH drops associated with swallowing.20 Finally, salivary pepsin levels have also been proposed as a potential method for assessing extension of reflux into the larynx and pharynx,22 but have yet to be studied in chronic cough.

Regardless of the latter, studies assessing proximal oesophageal reflux, which can be accurately assessed using MII/pH, have found no more reflux events in chronic cough patients than healthy controls.23,24 Probably more importantly, no correlation was found with the frequency of coughing,23 suggesting laryngopharyngeal reflux may not be a significant factor in chronic cough.

Microaspiration of reflux
The accurate measurement of markers of reflux microaspiration (such as pepsin and bile acids) in both saliva and airway (bronchoalveolar lavage, BAL) samples is technically very challenging and many of the available assays are insufficiently validated.24 To date studies measuring sputum/BAL pepsin25,25 and sputum bile concentrations, in patients with chronic cough have shown no significant differences from concentrations measured in healthy volunteers, suggesting aspiration of gastro-intestinal contents into the airways is also an unlikely cause for cough.

Oesophageal-Bronchial reflex
Both the oesophagus and airways/lungs are vagally innervated. As both these vagal pathways converge in the nucleus tractus solitaries (NTS) of the brain stem, stimulation of the oesophageal afferents has the potential to cross-activate the airway vagal innervation, and vice versa. This is termed the oesophageal-bronchial reflex and has been suggested by a number of investigators to be the most likely mechanism...
whereby reflux leads to cough.\textsuperscript{10,26,27} Ing \textit{et al} reported in a randomised, double-blind study that acid infusion into the distal oesophagus induced cough in the patients with chronic cough and reflux (pH study) but not healthy controls.\textsuperscript{28} These findings however were not reproduced in two subsequent studies of chronic cough patients with GORD,\textsuperscript{10,27} although Javorkova \textit{et al} did show an increase in cough sensitivity to inhalation of capsaicin (lowest concentration of capsaicin required to induce at least two coughs) which was not seen in healthy controls or GORD patients without cough,\textsuperscript{27} supporting oesophageal-airway cross-talk in patients with cough. Such cross-talk along with the observations that these patients can also often have impaired oesophageal motility\textsuperscript{28} and oesophageal clearance of refluxate\textsuperscript{29} might render them susceptible to even normal levels of gastro-oesophageal reflux.

The temporal associations between reflux and cough

If reflux does provoke cough and these symptoms do not just co-exist by chance, then both reflux and cough events should be expected to be temporally associated with one another. Such associations are evaluated using the symptom association probability (SAP)\textsuperscript{30} computed as $1 - p$, where $p$ is the probability that the number of cough and reflux events are associated by chance alone, and calculated using Fisher’s exact test. To be considered significant, SAP has to be $\geq 0.95$. A two-minute window for the SAP is commonly used to examine the association between typical oesophageal symptoms such as heartburn and reflux events.\textsuperscript{31} A similar window has been used to establish the temporal relationships between cough and gastro-oesophageal reflux episodes in a number of studies,\textsuperscript{5,9} but the appropriateness of the 2 minute window for defining reflux-cough associations remains in question and requires further investigation.

However, detecting coughing presents a significant challenge in such studies, and the inclusion of false events (e.g. throat clearing) and/or failure to detect all cough will lead to inaccurate representation of the associations between reflux and cough. Most studies to date have relied on cough diaries, patients pressing event recorders,\textsuperscript{6,32} and ambulatory oesophageal manometry\textsuperscript{6,23} to detect cough events. Each of these methods has significant limitations. Coughing recorded by patients in diaries or by pressing a button on pH/MII devices is likely to under-represent the actual numbers of coughs, as patients are unlikely to accurately document the hundreds of coughs that occur per day in chronic cough. These issues along with the fact that ambulatory manometry has not been validated for counting coughs outside of the laboratory setting\textsuperscript{9} suggests that SAP calculated using such techniques maybe somewhat questionable and might explain the variation in proportion of patients exhibiting a positive SAP between these studies.\textsuperscript{5,8}

The issue of accurate cough detection has recently been addressed by the development and use of acoustic cough recording. Smith \textit{et al} have used such an acoustic cough recorder to precisely measure cough events synchronised with impedance/pH to measure reflux.\textsuperscript{8} They showed that 48% of unselected chronic cough patients had positive SAP (2-min window) for reflux preceding cough (reflux-cough association). This percentage is higher than that reported in earlier studies and could be explained by previous work targeting patients in which extra-oesophageal disease had been excluded. However, in the study by Smith \textit{et al}, the presence or absence of extra-oesophageal diseases potentially contributing to cough did not predict SAP status, suggesting reflux may trigger cough irrespective of other diagnoses.

**Cough-reflux associations: a self-perpetuating cycle?**

In addition to the positive SAP for reflux preceding cough, a positive SAP for cough preceding reflux events (cough-reflux association) has been observed in 9 – 56% of chronic cough patients,\textsuperscript{6,8} depending on the measures used for recording cough and reflux as well as patients selection.

Proposed mechanisms include 1) elevation of the trans-diaphragmatic pressure associated with cough events forcing reflux to breach the LOS or 2) neurally mediated transient LOS relaxation (TLOSR) evoked by coughing. Reflux breaching the LOS would be expected to occur rapidly following coughing. However, in the study by Smith \textit{et al}, re-calculation of SAP for cough-reflux using a 10-second window, resulted in far fewer patients (24%) exhibiting a positive SAP.\textsuperscript{8} As this also accounted for just 6% of reflux events it seems unlikely that such a process is important.\textsuperscript{8} However, the observation that challenges to the airways can also have gastrointestinal consequences, such as increasing TLOSR and reflux events, in patients with asthma,\textsuperscript{35} does support the possibility of cough inducing reflux via TLOSR.

Significantly, the presence of a positive SAP for both cough-reflux and reflux-cough suggests the possibility of a self-perpetuating cycle.\textsuperscript{8,29,32} This may have therapeutic implications even if the reflux was not the initial triggering factor for cough, as it may still contribute to this self-perpetuating cycle of reflux inducing cough, inducing reflux.

**Evidence for sensitisation of the oesophageal-bronchial reflex**

The observation that infusion of acid into the oesophagus appears to have no effect on cough reflex sensitivity in patients with objectively confirmed GORD without cough, but sensitises the cough reflex in chronic cough patients with GORD\textsuperscript{27} suggests that the oesophageal bronchial reflex maybe sensitized at least in some patients with chronic cough. This is supported by the observation of Smith \textit{et al} that SAP positive patients have both increased cough reflex sensitivity and cough rate compared with SAP negative patients, despite similar degrees of gastro-oesophageal reflux.\textsuperscript{8} Moreover, a central rather than peripheral sensitization process is supported by the findings that SAP positive patients have no more oesophagitis than SAP negative patients.\textsuperscript{8}

It is unclear what initiates central sensitisation and why some patients with chronic cough exhibit features in keeping with this phenomenon (reflux-cough associations) whilst others do not. Many patients with chronic cough also report that exposure of their airways to innocuous stimuli such as perfumes and even talking triggers coughing.\textsuperscript{26} In much the same manner, subjects with reflux-cough associations are demonstrating a similar lowering of the threshold for coughing such that relatively normal levels of oesophageal reflux triggers cough.

**Conclusion**

Gastro-oesophageal reflux events remain an important factor in the pathogenesis of patients with chronic cough even with physiological amount of reflux. Moreover, the oesophageal-bronchial reflex is likely to play a key role in the pathophysiology of reflux associated cough.

Further research is needed to understand the mechanisms leading to sensitisation of the cough reflex in gastro-oesophageal reflux associated cough. Well-designed clinical trials are needed,
testing agents specific for neuronal targets likely to be mediating the oesophageal-bronchial reflex pathways and/or the neural sensitisation mechanisms.

References


