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Gastro-oesophageal reflux and tachykinins

Gastro-oesophageal reflux and tachykinins in asthma and chronic cough

Alyn H Morice

A possible new therapeutic option

There is no doubt that gastro-oesophageal reflux can cause a chronic cough. However, how frequently reflux is the underlying cause in patients presenting to the readers of *Thorax* is a matter of much debate. This confusion can be laid squarely at the door of the gastroenterologists who have taken one symptom of acidic reflux—heartburn—and made it the sine qua non for gastro-oesophageal reflux disease. This characterisation of gastro-oesophageal reflux disease as heartburn has led to the denial of the non-acid extra-oesophageal symptoms of reflux. In reality, however, reflux is almost universal in humans because our upright posture has disrupted the anatomy of the lower oesophageal sphincter. Measurement of electrical impedance within the gullet in fact shows that only a small number of reflux episodes are acidic (below pH 4)[1] and, while it takes a lot of acid to burn the hardy oesophagus, anyone who has performed a bronchoscopy will know that the delicate larynx and airways respond to the most gentle of stimulation. The difference between reflux causing respiratory symptoms and gastro-oesophageal reflux disease is neatly demonstrated by cough after meals. Patients with postprandial reflux cough do so approximately 10 min after food.[2] This is the time of peak transient opening of the lower oesophageal sphincter and combats aerophagy. However, heartburn does not occur until later because stomach acid has been neutralised by the meal.

What evidence is there that reflux is an important cause of chronic cough? In a recent survey of normal subjects, Ford *et al*[3] found that 7% reported a chronic cough sufficient to interfere with activities of daily living. After correction for factors such as cigarette smoking, gastrointestinal symptoms including regurgitation and irritable bowel (but not heartburn) were highly correlated with cough. However, as with cigarette smoking and lung cancer, epidemiology can never prove a causal link—merely suggest associations. Can we be sure if there is no specific diagnostic test? The answer is not yet but, for the clinician, the precipitation of cough by factors known to cause transient opening of the lower oesophageal sphincter such as rising, phonation and postprandially gives the game away. Other extra-oesophageal symptoms such as dysphonia, rhinitis and a funny taste in the mouth are also present in subjects with cough with proven reflux disease.[2]

The approach taken in this latter study, to explore the symptoms of reflux cough by assessing patients with proven acid reflux, has been adopted in a study by Patterson and colleagues published in this issue of *Thorax* (***see p 491***).[4] They investigated the profile of tachykinins present in induced sputum from patients with asthma (as defined by bronchial lability) and patients with cough without reversibility or methacholine hyperresponsiveness. They performed 24 h pH monitoring to define those in each group who had acid reflux and found that patients with acid reflux had higher tachykinin levels. Of the several possible explanations for this phenomenon, they favour the reflex neurogenic release of the peptides. What is very interesting about this study is that, for the first time, a difference has been detected in the profile of patients with different phenotypes of cough. When patients with chronic cough have previously been studied by histological examination,[5] induced sputum inflammatory markers[6 7] or neurotrophin profiles,[8] no difference has been detected, suggesting to some that chronic cough is a single syndrome. While this is still possible, and acid reflux may be merely stimulating an epiphenomenon of tachykinin release, this is the first study to define a unique phenotype which may have important consequences for treatment. Current treatment for reflux of respiratory importance is less than satisfactory. Because this sort of reflux is less acid-dependent, even twice daily proton pump inhibitors only produce a response in at most half of patients. Unsurprisingly, drugs that act on the motility of the gullet such as metaclopramide and domperidone can produce pleasing responses. Baclofen, which mimicks vagal inhibition of lower oesophageal sphincter opening, is our last specific treatment for reflux cough. The finding of higher levels of tachykinins in sputum from patients with acid reflux-related asthma and cough suggests an urgent need for neurokinin antagonists to be studied in these patients.

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Systemic inflammation and progression of COPD

Systemic inflammation and progression of COPD

Jørgen Vestbo

The role of C-reactive protein

C-reactive protein (CRP) is considered one of the key markers of systemic inflammation in chronic obstructive pulmonary disease (COPD) and currently receives a lot of attention. In their systematic review of systemic inflammation in COPD, Gan *et al* showed that CRP was associated with the level of forced expiratory volume in 1 s (FEV_1) in the five studies included in the review,[1] and two recent studies using fairly large populations of well-characterised patients with COPD have shown a strong association between increased CRP levels and prognosis.[2 3] Sin and Man have previously shown that raised levels of CRP were associated with cardiac injury in COPD[4] but, in the two recent studies, the association between CRP and mortality was not merely driven by an associated risk of cardiovascular deaths.[2 3]

In this issue of *Thorax* (***see p 515***) Fogarty *et al* examine the association between CRP and FEV_1 in more detail.[5] Using data on 2633 randomly selected adults from Nottingham in 1991 and followed up in 2000, they looked at both cross-sectional and longitudinal associations between CRP and FEV_1. At both the 1991 and 2000 survey there was a clear inverse association between the level of FEV_1 and CRP, with a difference in FEV_1 between the highest and lowest deciles of CRP of 381 ml and 259 ml in 1991 and 2000, respectively. The association was strongest in underweight subjects, defined as those with a body mass index (BMI) <20 kg/m^2. Data from 1343 subjects were available for analyses of FEV_1 decline and, in this population, there was no association between CRP at either time point and 9 year change in FEV_1.

There are currently only limited data with which to compare these findings. In a smaller French study of 531 subjects, there was a tendency towards a steeper decline in FEV_1 over the 8.5 year follow-up in the tertile with highest CRP at baseline ($p = 0.14$).[6] In this study by Shaaban *et al*, subjects with increasing CRP levels during follow-up had steeper declines in FEV_1 than those with stable or decreasing CRP levels, but it is not possible to imply causality from associations between parallel changes. Other markers of systemic inflammation do not seem to help us much. Dahl *et al*[7] looked at fibrinogen in a Danish cohort and found an association between fibrinogen level and level of FEV_1, preceding decline in FEV_1 and subsequent hospital admission. In fact, based on these findings it would be tempting to look at systemic inflammation more as a consequence of COPD than an active component alongside inflammation in the airways and lung parenchyma. An indicator of an effect of systemic inflammation on decline in lung function comes from a clinical study of COPD patients with and without hepatitis C.[8] In this study, Kanazawa *et al* found a steeper decline in FEV_1 in patients with hepatitis C than in uninfected controls, independent of smoking habits. In addition, patients with hepatitis responding to interferon-α treatment had slower declines than those not responding, a response defined as disappearance of HCV RNA. Although the number of patients was very limited (59 in total), these findings leave open the possibility that systemic inflammation may be linked to progression of airflow limitation.

The systemic effects of COPD are more straightforward than the role of systemic inflammation on disease progression. In particular, weight loss and loss of fat-free mass become increasingly apparent with increasing severity of COPD, and both a low BMI and a low fat-free mass index have been shown to be strong predictors of mortality in COPD.[9–11] Studies have linked systemic inflammation with loss of both body mass and fat-free mass[11–14] but, in the largest study,[11] the association did not seem impressive and it is likely that other factors also play a role for weight loss. Bolton *et al*[15] found a strong association between markers of systemic inflammation and loss of fat-free mass as well as bone density, but the severity of the patients studied (mean FEV_1 1.0 litres) makes it difficult to determine whether the findings seen are anything but the consequences of disease progression. Whether the fact that fat-free mass depletion is seen even in early disease[11] indicates a role for systemic inflammation earlier than suggested above—at least in a subgroup of patients—remains to be seen.

In the most recent GOLD guidelines there has been more emphasis on extrapulmonary effects as part of COPD, and systemic features are included in the chapter on pathology, pathogenesis and pathophysiology. It is very likely that systemic inflammation plays a key role in the development of systemic manifestations of COPD and that this should impact on our approach to the disease as suggested in a recent review.[16] However, as the study by Fogarty *et al* shows, we are still far from fully understanding the role of systemic inflammation in COPD.

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