Airway reflux, cough and respiratory disease

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Abstract: It is increasingly accepted that the effects of gastro-oesophageal reflux are not limited to the gastrointestinal tract. The adjacent respiratory structures are also at risk from material ejected from the proximal oesophagus as a result of the failure of anatomical and physiological barriers. There is evidence of the influence of reflux on several respiratory and otorhinological conditions and although in many cases the precise mechanism has yet to be elucidated, the association alone opens potential novel avenues of therapy to clinicians struggling to treat patients with apparently intractable respiratory complaints. This review provides a description of the airway reflux syndrome, its effects on the lung and current and future therapeutic options.

Introduction

The relationship between gastro-oesophageal reflux (GOR) and respiratory disease is controversial. There is no doubt that the lungs can suffer damage as a direct result of aspiration of gastric contents causing a chemical injury, but aspiration pneumonitis is merely the most obvious clinical manifestation of a more complex and diverse process. GOR can be the primary cause of respiratory symptoms such as chronic cough and can also complicate established respiratory disease.

The terminology employed to describe GOR affecting the respiratory tract is varied and contributes to the lack of clarity in diagnosis. Laryngopharyngeal reflux (LPR) is recognised as a distinct clinical entity caused by reflux of gastric contents to the laryngopharynx [Pontes and Tiago, 2006]. A similar condition with fluoroscopic oesophageal abnormalities has been termed esophagopharyngeal reflux [Belafsky *et al.* 2008] and the cumbersome alternative terms supraoesophageal and extraoesophageal reflux also encompass the effects of gastric content entering the remainder of the upper respiratory tract [Wiener *et al.* 2009; Koufman *et al.* 2002]. We prefer the simpler term 'airway reflux' to describe the broader phenomenon.

Evolution of humans into upright, bipedal organisms has led to a unique predisposition to GOR and consequent aspiration. Recent advances in characterisation of the pathophysiology, including both the composition of the refluxate, which can be gaseous and nonacid, and the mechanisms of damage to the respiratory epithelium have led to insights into the development of clinical manifestations in the upper and lower respiratory tracts. We present an overview of the syndrome which, when recognised, makes a wide variety of therapeutic options available to the clinician.

Epidemiology

The association of GOR with various respiratory conditions is well described in epidemiological studies. The diagnostic criteria used are diverse, ranging from acid reflux symptoms coexisting with asthma and other respiratory symptoms as in the Nord-Trøndelag Health Survey [Nordenstedt *et al.* 2006] to the presence of erosive oesophagitis or strictures as investigated by el-Serag and Sonnenberg [El-Serag and Sonnenberg, 1997] in a retrospective review of over 100,000 cases. The latter study found positive associations with sinusitis, aphonia, laryngitis and laryngeal stenosis in the upper respiratory tract as well as lower tract features such as chronic bronchitis, asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, bronchiectasis, pulmonary collapse and pneumonia. Smaller studies have shown that the presence of a hiatus hernia or reflux oesophagitis is associated with an increased likelihood of respiratory related hospitalisation [Ruhl *et al.* 2001] and the RHINE study group demonstrated that nocturnal GOR is independently associated with the onset of asthma and respiratory symptoms [Gunnbjörnsdóttir *et al.* 2004]. Data from a

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cross-sectional questionnaire survey of 4000 patients in Yorkshire showed a relationship between chronic cough, regurgitation and irritable bowel syndrome [Ford *et al.* 2006].

Whether the relationship is causal or coincidental is difficult to determine from retrospective studies. Analysis from the prospective ProGERD study [Jaspersen *et al.* 2003] found a high prevalence (32.8%) of extraoesophageal symptoms developing in patients presenting with heartburn which was significantly higher in patients with erosive oesophagitis, particularly in those with more severe endoscopic grading of oesophageal disease implying an exposure–response relationship.

The use of acid-related GOR disease and symptomatology as a marker may in fact underestimate the true prevalence of airway reflux but the diversity of clinical manifestations and lack of a reliable diagnostic test precludes direct study.

Pathophysiology

Reflux reaches the airway as a result of an inherent susceptibility to the condition in humans combined with the failure of physiological defence mechanisms. Several components of gastric contents then have the potential to stimulate sensory receptors and trigger respiratory symptoms.

Evolutionary disadvantages

Two factors in human evolution, which are significant in terms of survival advantage, mean we are uniquely predisposed to airway reflux. Firstly, the relatively rapid transition to bipedal locomotion was not matched by compensatory changes in the gastrointestinal tract. In other mammals, the oesophagus is near horizontal, with food boluses dropping into the vertically hanging stomach as they traverse the diaphragm. In humans, the upper gastrointestinal tract is straightened out, removing the anatomical barrier preventing reflux when the lower oesophageal sphincter (LOS) opens. The crura of the diaphragm partially compensate by creating a bend in the lower oesophagus, but using a mobile structure to accomplish this has drawbacks; reflux on phonation is common, particularly with laughing as the intra-abdominal pressure oscillates. An even more significant evolutionary advantage is the development of speech and language, but this has also increased the risk of aspiration because of the changes in the laryngeal sphincter. The deepening of the larynx and separation of the soft palate from the epiglottis and arytenoids leaving the oropharynx permanently expanded is particularly ineffective at preventing transit of material, either from the oral cavity or regurgitated from the stomach [Laitman and Reidenberg, 1997].

Physiological defences

Despite the evolutionary predisposition, reflux is not universal. There remain barriers which prevent the free transit of gastric material to the airway, namely the lower and upper oesophageal sphincters. Abnormalities of these increase the likelihood of symptomatic GOR or airway reflux, for example patients with a hiatus hernia are inherently more susceptible to GOR because of the malposition of the LOS in the thoracic cavity with the consequent loss of the diaphragmatic component of sphincter tone. LOS hypotonia and an increased frequency of transient LOS relaxation (TLOSR) episodes are the principle mechanisms thought to contribute to GOR, with studies suggesting that the former is the more significant factor for reflux to the proximal oesophagus [Grossi *et al.* 2001]. There is also evidence which points to TLOSR as a likely culprit, particularly in airway reflux. The episodes are detectable in normal controls, with early investigations in asymptomatic volunteers demonstrating up to 24 episodes related to TLOSRs over a 12 h period [Dent *et al.* 1980]. Increased TLOSR frequency was thought to be contributory to the development of GOR symptoms, however more recent work suggests that there is no difference in the frequency between patients and controls [Trudgill and Riley, 2001]. In the latter study, there was also no difference in the number of reflux episodes detected using intraluminal pressure monitoring but episodes in patients with GOR were more frequently associated with a drop in pH, suggesting that acidity of the reflux is key to the development of the classical GOR symptom of dyspepsia. Clearance of acid from the oesophagus and a return to baseline pH is considered a useful marker of oesophageal function [Helm, 1986]. Postma and colleagues used dual probe pH monitoring to show that oesophageal pH returns to normal more quickly in patients with LPR alone than in those with GOR [Postma *et al.* 2001]. The authors concluded that patients with LPR alone had superior oesophageal function; however they also found that the LPR group had a longer clearance time than normal controls. The degree of acidity does not seem to affect the opening of the upper oesophageal sphincter (UOS) which is normally associated with TLOSR episodes and

changes in oesophageal intraluminal pressure [Pandolfino *et al.* 2007]. Investigation of patients with chronic cough showed a third of patients had normal pH studies despite abnormal oesophageal manometry [Kastelik *et al.* 2003]. Taken together, these data support two distinct pathophysiological phenotypes. Acidic reflux causing classical GOR with heartburn, related to LOS hypotonia or anatomical abnormalities, and nonacid, gaseous reflux related to TLOSR episodes and leading to airway reflux.

Reflux composition

Gaseous reflux has been well described with studies using multichannel impedance monitoring showing over a third of normal controls having reflux with a detectable gaseous component. Unsurprisingly, the gaseous material was more likely to reach the proximal oesophagus than the liquid component, suggesting that it is the more likely mechanism of airway reflux [Balaji *et al.* 2003]. This raises the question of whether the damaging agent in reflux can be acid alone since the pH of gaseous reflux can be mildly acidic [Kawamura *et al.* 2004]. Studies in the oesophagus have shown that the mucosal effects are similar on perfusion with acidic and nonacid solutions [Farré *et al.* 2010] and that bile exposure is commonly present in patients with severe mucosal damage and is associated with worse oesophageal dysfunction [Oh *et al.* 2006]. Experimental exposure of laryngeal epithelial cells to pepsin has shown uptake and cell damage at pH 7.4 [Johnston *et al.* 2009], illustrating that damage to airway epithelium can indeed occur as a response to nonacid reflux. The question of how airway damage can occur despite a lack of apparent oesophageal symptoms can be explained by the increased susceptibility of the airway to damage compared with the robust oesophageal mucosa. Experimental evidence shows that carbonic anhydrase III activity is increased in the oesophagus in patients with GOR, theoretically providing a defence mechanism against acid injury, but this activity is reduced in the laryngeal tissue of patients with LPR [Axford *et al.* 2001]. Other mechanisms such as depletion of E-cadherin cell adhesion molecules may also contribute [Johnston *et al.* 2003].

Cough reflex hypersensitivity

The process by which reflux causes respiratory symptoms, and in particular chronic cough is likely to be a combination of a heightened sensitivity to cough stimuli and the recurrent trigger of

reflux episodes. Coughing is a physiological defence mechanism which is thought to be neurogenically mediated via transient receptor potential (TRP) ion channels on airway sensory neurones (Figure 1). The vanilloid sensitive (TRPV1) receptor is present in the airway [Watanabe *et al.* 2005] and is stimulated by a group of compounds which includes capsaicin, a substance derived from chilli peppers used as a tussive agent in cough challenge testing [Midgren *et al.* 1992]. It is also activated by acid [Bevan and Gepetti, 1994], providing a link both to the use of citric acid as a cough stimulant and to acidic reflux events. The molecularly similar TRPA1 (ankyrin) receptor is coexpressed with TRPV1 [Story *et al.* 2003] and is stimulated by several other substances including foodstuffs [Jordt *et al.* 2004] which have potential significance in nonacid reflux. Both receptors have
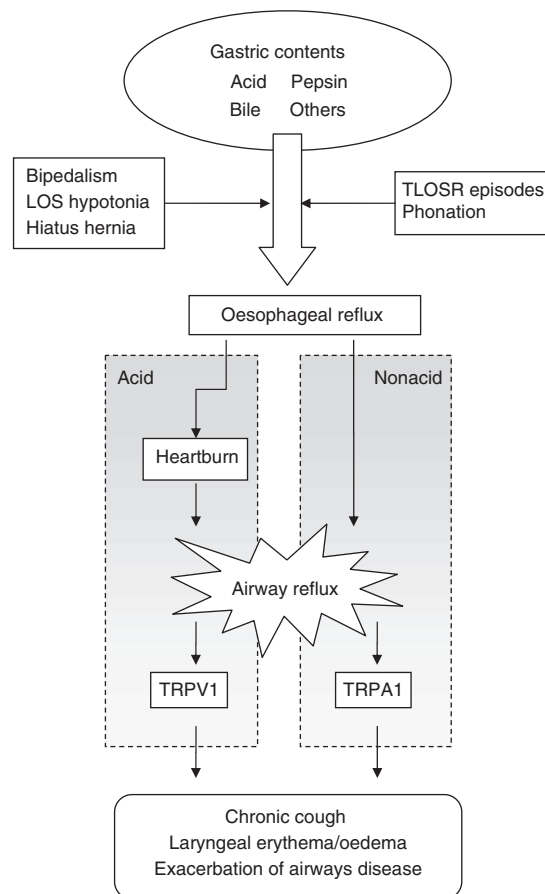

Figure 1. Proposed mechanism of reflux to the airway causing respiratory symptoms. LOS, lower oesophageal sphincter; TLOSR, transient lower oesophageal sphincter relaxation; TRPA1, transient receptor potential (ankyrin receptor); TRPV1, transient receptor potential (vanilloid sensitive).

been shown to contribute to neurogenic inflammation in animal studies [Wei *et al.* 2010; Trevisani *et al.* 2004a]. Expression of TRPV1 is increased on afferent neurones in the respiratory tract in patients with chronic cough [Mitchell *et al.* 2005] and also in patients with oesophagitis [Matthews *et al.* 2004].

Capsaicin cough sensitivity increases in response to upper respiratory tract infection [O'Connell *et al.* 1996] and has also been demonstrated in patients with asthma, COPD [Doherty *et al.* 2000a] and fibrosing alveolitis [Doherty *et al.* 2000b]. TRPV1 anatagonists have been shown to reduce cough frequency experimentally [Trevisani *et al.* 2004b] and have the potential to become useful therapeutic agents in clinical practice.

Respiratory disease and airway reflux

The association of clinical respiratory symptoms and reflux has been investigated from several perspectives and as a consequence is marred with confusing terminology. The gastroenterological view is of extraoesophageal manifestations appended to the spectrum of GOR disease, while the respiratory-biased reflux cough and reflux asthma syndromes focus on the effects rather than the cause of airway reflux [Vakil *et al.* 2006]. Laryngopharyngeal reflux sits both anatomically and physiologically between the two. A closer inspection reveals a common symptomatology between all three groups, with complaints such as globus, throat clearing and soreness, dysphonia, an unpleasant or metallic taste in the throat and often a chronic intractable cough featuring prominently [Everett and Morice, 2007; Pontes and Tiago, 2006]. More typical symptoms of breathlessness and wheeze and the corresponding heartburn and dysphagia can be absent, with estimates ranging from 30% to 75% of the time [Everett and Morice, 2007; Jaspersen *et al.* 2006; Irwin *et al.*1990] and are thus less useful in diagnosis.

Chronic cough

The most ubiquitous symptom of airway reflux is chronic cough, often occurring in the absence of heartburn [Jaspersen *et al.* 2006]. The precise mechanism is again a matter of debate. Impairment of laryngopharyngeal mechanosensitivity has been demonstrated [Phua *et al.* 2005] and there is also evidence that weakly acidic reflux can be significant [Pauwels *et al.* 2009]. In our own survey, regurgitation rather than heartburn was most strongly associated with

cough [Ford *et al.* 2006]. Although patients with chronic cough have not been shown to have an increased frequency of reflux episodes, there is evidence that nonacid reflux events reach the pharynx more often in patients when there is a positive symptom association probability (SAP) between cough and oesophageal reflux episodes [Patterson *et al.* 2009]. A validated questionnaire (available at www.issc.info) has been developed to capture the symptom complex associated with airway reflux induced cough [Morice *et al.* 2011].

Asthma

Asthma is a heterogeneous entity with few adult patients conforming to the typical childhood atopic phenotype. In cough-variant asthma, isolated chronic cough may be the only presenting feature, with the final diagnosis being dependent on a response to antiasthma therapy [Dicpinigaitis, 2006]. Difficult asthma is often thought to be principally related to poor adherence to treatment. However, GOR and microaspiration may contribute to airway inflammation and exacerbation in allergic asthma [Spaulding *et al.* 1982; Mays, 1976] and patients with GOR may develop eosinophilic airway hypersensitivity and an asthma-like syndrome characterised by unpredictable paroxysms of coughing, wheezing and breathlessness [Kiljander and Laitinen, 2004] which suggests a degree of overlap between typical or cough variant asthma and reflux-induced chronic cough. Up to 80% of patients with asthma have been found to have abnormal acid reflux on 24 h pH monitoring [Sontag *et al.* 1990] and tracheal aspiration has also been demonstrated [Jack *et al.* 1995]. Wu *et al.* [2002] showed an increase in capsaicin challenge cough sensitivity in response to acid perfusion of the oesophagus in patients with mild asthma and chronic cough.

Recent work has revealed a potential link between airway hypersensitivity and GOR with increased airway tachykinin levels found in induced sputum samples from patients with asthma and chronic cough [Patterson *et al.* 2007]. Tachykinin-mediated neurogenic inflammation has been suggested as a mechanism in the development of a response to inhaled irritants and is potentially important in patients with asthma [Barnes, 2001]. Paradoxically, treatments for asthma may also worsen reflux, with theophyllines [Berquist *et al.* 1981] and beta-2

adrenoreceptor agonists [Lacy *et al.* 2008] having the potential to reduce the LOS pressure.

Chronic obstructive pulmonary disease

Patients with established lung disease are likely to be more susceptible to the effects of airway reflux. Patients with COPD have a high prevalence of reflux into the proximal oesophagus, perhaps contributed to by the changes in thoracic anatomy seen in the later stages of the condition. Interestingly, only a minority of patients studied reported typical heartburn [Kempainen *et al.* 2007; Casanova *et al.* 2004]. The combination of LPR symptoms and laryngoscopic findings with COPD has also been investigated with the dual diagnosis made in 44% of patients studied [Eryuksel *et al.* 2009]. Many patients with COPD are recurrently admitted to secondary care in exacerbation with no clinical evidence of acute infection. If a proportion of these are due to airway reflux, a new and potentially important avenue of treatment becomes available for these highly resource consuming patients.

Cystic fibrosis

An increased prevalence of symptomatic GOR is well documented in patients with cystic fibrosis [Blondeau *et al.* 2008a]. Recent work shows this may persist despite acid suppression therapy and can be associated with worsening of respiratory symptoms [Sabati *et al.* 2010]. Objective measurements have demonstrated abnormal oesophageal function with reduced LOS pressures and positive 24 h pH studies [Ledson *et al.* 1998].

Interstitial lung disease

Numerous studies have shown an association between GOR and interstitial lung disease (ILD) based on an association with hiatus hernia [Mays *et al.* 1976] and demonstrable reflux on pH monitoring [Salvioli *et al.* 2006]. Chronic microaspiration has been suggested as a mechanism, although the specific pathophysiology, particularly in relation to the newer definitions of ILD, has yet to be determined [Lee *et al.* 2010]. ILD, and in particular usual interstitial pneumonia, is generally a progressive disease with few effective treatments available. Confirmation of an airway reflux aetiology would again provide new options.

Other respiratory disease

Links have been made between the presence of airway reflux and several other respiratory diseases, however whether this simply a chance finding or a causal relationship requires further study.

Obstructive sleep apnoea has been associated with chronic cough, with changes in nocturnal oesophagaeal function demonstrated. Interestingly these appear to be protective against reflux [Kuribayashi *et al.* 2010] despite obesity being a major risk factor for both obstructive sleep apnoea and GOR [Jacobson *et al.* 2006]. Both acid reflux and nonacid reflux are prevalent in lung transplant recipients [Blondeau *et al.* 2008b] and early development of the bronchiolitis obliterans syndrome causing chronic rejection is associated with the presence of bile acids in bronchoalveolar lavage fluid [D'Ovidio *et al.* 2006].

Otorhinological manifestations

The diagnosis of laryngopharyngeal reflux (LPR), the most frequently used descriptor, is essentially a clinical one based on typical symptoms of globus pharyngeus, dysphonia, excessive throat clearing and soreness [Pontes and Tiago, 2006]. In addition, endoscopic visualisation and scoring of the laryngeal appearance [Belafsky *et al.* 2001] is used to exclude malignancy and assess for abnormalities. Features of vocal cord oedema with mucosal abnormalities of the cords and intra-arytenoid notch were found to reliably distinguish symptomatic cases from controls [Jonaitis *et al.* 2006]. It is comparatively widely recognised by otolaryngologists and commonly treated with proton pump inhibitors (PPIs) [Karkos *et al.* 2007].

Investigation

To date, there is no gold standard test to confirm the presence of airway reflux or to clearly differentiate it from other causes of respiratory symptoms. Eliciting the characteristic clinical features, with an empirical trial of antireflux medication is the mainstay of the current diagnostic process. A successful trial of high-dose proton pump inhibitor was considered diagnostic and is recommended in guidelines for chronic cough [Morice *et al.* 2007] and LPR [Koufman *et al.* 2002]. Recent work however suggests that this may be unreliable, even in patients with classic GOR symptoms [Aanen *et al.* 2006].

The detection of pepsin by immunoassay in sputum has been shown to be highly specific and sensitive for LPR (diagnosed by dual probe oesophageal pH monitoring) [Knight *et al.* 2005] and this noninvasive test may prove to be a useful marker of airway reflux and could be extended to

other respiratory samples, such as exhaled breath condensate or bronchial lavage.

More invasive methods of investigation such as oesophageal pH monitoring and laryngoscopic examination are used in clinical practice and may have some utility, with studies suggesting that patients with LPR may be differentiated from controls using upper oesophageal acid exposure time [Merati *et al.* 2005], although other investigators have found no difference in symptoms in patients with and without proximal acid exposure [Cool *et al.* 2004]. The sensitivity and specificity of oesophageal pH monitoring and laryngoscopic examination may be lacking however and they cannot be considered diagnostic of airway reflux [Oelschlager *et al.* 2005; Vaezi, 2003]. The concept of using oesophageal pH alone as a marker of reflux has inherent failings because of the effects of nonacid and gaseous reflux. Combined monitoring with electrical impedance shows that nonacid reflux continues despite acid suppression [Zerbib *et al.* 2008; Mainie *et al.* 2006) and may be a mixture of liquid and gas which is associated with respiratory symptoms regardless of pH [Tutuian *et al.* 2008]. New techniques for directly measuring the pH of aerosolised liquids in the pharynx using a minimally invasive probe are promising. We have shown that gaseous reflux events can be detected using this system in patients with normal conventional oesophageal physiology and despite Nissen fundoplication [Molyneux *et al.* 2010a]. Current analysis however relies on the pharyngeal pH crossing a lower threshold as a marker of a reflux event, with normal values having been defined in an asymptomatic population [Ayazi *et al.* 2009]. This has similar limitations to oesophageal pH monitoring in that nonacid reflux events responsible for airway symptoms would not be detected. An alternative system based on variation in pH as a marker of reflux events is in development with initial results suggesting that different disease phenotypes may show different patterns of pH variation [Molyneux *et al.* 2010b].

Therapy

The established therapy for typical gastro-oesophageal reflux is less effective in airway reflux for reasons which are outlined below. Nevertheless, the complex pathophysiological process involved yields several therapeutic targets. Novel approaches are necessary but most can be accomplished with simple interventions, often using established, inexpensive medication.

Pharmacological agents

PPIs and histamine receptor antagonists are well established as the mainstay of therapy for typical GOR with heartburn symptoms or peptic ulceration. Both have been recommended [Pratter *et al.* 2006] and are widely used for a variety of airway reflux manifestations. There is some evidence of an effect, for instance a reduction in capsaicin cough sensitivity with omeprazole was demonstrated in patients with asthma [Ferrari *et al.* 2007] but a recent randomised trial showed no effect of PPIs in poorly controlled asthma [Mastronarde *et al.* 2009]. The authors concluded that reflux was not a significant contributor to poor asthma control, however the study proves only that acid reflux is not relevant. Several studies have failed to demonstrate an effect on LPR using PPI compared with placebo. A recent Cochrane review of PPI in chronic cough, the most common airway reflux syndrome, concluded that there was insufficient evidence of benefit from a number of small, uncontrolled trials and noted a strong placebo effect [Chang *et al.* 2006]. A randomised trial was recommended; we have recently completed such a project using twice daily esomeprazole which showed no benefit over placebo overall and suggests that any treatment effect is limited to patients with typical heartburn symptoms (unpublished data).

It is unsurprising that acid suppression alone is insufficient to prevent airway reflux because, as already described, nonacid and gaseous reflux may be more closely related to airway symptoms in contrast to the acid injury mechanism of typical GOR. A more rational approach is to target the failed mechanical barriers to reflux such as TLOSR episodes. TLOSRs are under vagal control [Mittal *et al.* 1995] and can be inhibited by cholinergic blockade with atropine. Peripheral anticholinergics are ineffective, implying a central mechanism [Fang *et al.* 1999], but vagal mechanoreceptors at the LOS respond to gastric distension and can be inhibited by gamma-aminobutyric acid (GABA) type B receptor agonists and metabotropic glutamate type 5 receptor (mGluR5) antagonists [Blackshaw, 2008]. Baclofen is an analogue of aminobutyric acid which is widely used for muscle spasticity in multiple sclerosis and other neuromuscular conditions. It has been shown to significantly reduce the frequency of TLOSR [Holloway, 2001] but has a problematic side effect profile. It is our normal practice to use low doses starting at

5 mg three times daily. Lesogaberan, a GABA(B) agonist currently in development, may avoid the adverse central nervous system effects [Bredenoord, 2009] and can also reduce TLOSR frequency and increase LOS pressure [Boeckxstaens *et al.* 2010]. It has the potential to become the preferred agent for reducing TLOSR frequency if tolerance is superior to baclofen in practice. mGluR5 antagonists have also shown promise in animal studies with 60–90% reduction in TLOSR episodes demonstrated experimentally [Jensen *et al.* 2005].

Prokinetic agents such as metoclopramide and domperidone as well as macrolide antibiotics such as erythromycin are used in the critical care setting in patients receiving enteral nutrition. Improving gastric motility and preventing delayed gastric emptying reduces the likelihood of reflux and aspiration [Deane *et al.*2009]. A study on patients with reflux cough showed that a third of patients not responding to PPI improved with the addition of metoclopramide or cisapride [Poe and Kallay, 2003]. The latter agent has been withdrawn from the market because of a link to long QT syndrome leaving metoclopramide and domperidone as the first-choice agents. Domperidone may be the better option because it avoids the extrapyramidal side effects of metoclopramide and can be used for longer term therapy. Both are used at standard doses of 10 mg three times daily. Low-dose erythromycin (250 mg twice daily) is widely used for motility therapy and the newer macrolide azithromycin has been shown to reduce proximal reflux events, oesophageal acid exposure and bile aspiration in lung transplant recipients [Mertens *et al.* 2009].

As a consequence of the variable contributions of the different pathophysiological factors, there is no single agent which is effective for all patients. Because of this, we recommend a series of therapeutic trials of each agent, normally for a period of 4 weeks as long as the initial doses are well tolerated. The current lack of a definitive objective test for airway reflux means that any beneficial effect has to be assessed subjectively by the patient.

Nonpharmacological methods
The simplest method for the clinician to suggest is perhaps the most difficult for the patient to achieve; weight loss reduces the tendency to reflux and carries associated benefits in reducing the load on the respiratory system. More specific measures can be suggested, such as avoidance of large meals and carbonated drinks as gastric distension stimulates TLOSR episodes [Scheffer *et al.* 2002]. Caffeine and nicotine both worsen reflux [Pandolfino and Kahrilas, 2000; Boekema *et al.* 1999] but whether reducing caffeinated beverage intake or smoking cessation are effective as a treatment modality for airway reflux is difficult to quantify.

At the opposite end of the risk spectrum, surgical procedures are also an option to treat airway reflux. Laparoscopic Nissen fundoplication is well established as a safe and effective treatment for typical GOR [Broeders *et al.* 2010] and there is increasing evidence of its effectiveness in treating chronic cough and other respiratory symptoms [Fathi *et al.* 2009; Farrell *et al.* 2001; Allen and Anvari, 1998]. In the obese, a Roux-en-Y gastric bypass may be a more effective alternative with the combined benefits of weight loss and concurrent improvement in the mechanical barriers to reflux [Ikramuddin, 2008].

Conclusion
Airway reflux is a widespread condition with a characteristic combination of symptoms. It is clearly associated with various lung diseases and ongoing research is providing new insights into the pathological mechanisms involved. Current investigations are limited but provide supporting evidence for the diagnosis and new modalities are becoming available.

Recognition of the syndrome can open a variety of therapeutic possibilities to the clinician for patients who may have been labelled as intractable. The diagnosis should be considered in patients with chronic unexplained cough or episodic breathlessness in the presence of an unpleasant taste in the throat, excessive throat clearing and soreness, globus or dysphonia. Current pharmacotherapy utilises established, inexpensive drugs and there is potential for significant symptomatic improvements in patients with established respiratory disease. Further study is needed to develop more precise methods to identify patients with significant airway reflux and to investigate the effects of therapy.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this manuscript.

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