

## Airway reflux: an emerging topic in respiratory medicine



More than a century ago, Canadian physician William Osler observed that “severe paroxysms may be induced by overloading the stomach” in patients with asthma.<sup>1</sup> In these patients, the key mechanism involved would have been gastro-oesophageal reflux reaching the bronchi. Brief exposure to acid does not damage the oesophagus, and up to 50 reflux episodes a day of acid weaker than pH4 might be considered normal; however, when reflux material—composed of pepsin, hydrochloric acid, bile salts, proteolytic enzymes, partly digested food, and bacteria—goes beyond the oesophagus and enters the upper airways, it is known as airway reflux, extra-oesophageal reflux, or silent reflux, so-called because up to 70% of individuals with the condition do not report retrosternal burning or acid regurgitation.

In humans, two evolutionary features have made it easier for reflux material to enter the airways: the development of language (the larynx increased in size and descended to lie adjacent to the top of the oesophagus) and bipedalism (the connection between the oesophagus and stomach evolved from a right angle to a straight line).

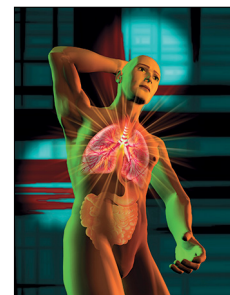
The associations between gastro-oesophageal reflux and various extra-oesophageal problems were presented in the 2006 Montreal consensus document,<sup>2</sup> which distinguished between established associations with gastro-oesophageal reflux (cough, laryngitis, asthma, and dental erosions) and proposed associations (sinusitis, idiopathic pulmonary fibrosis, and recurrent otitis media). Association, of course, is not the same as causality. 1 year after the Montreal consensus, the finding that lung transplant rejection could be caused by damage from reflux material sparked substantial interest.<sup>3</sup> Opinion on this relationship between airway reflux and airway diseases is still developing: epidemiological evidence of this association is undeniable,<sup>4,5</sup> but the cause–effect relationship remains unclear. In a review on the connections between asthma and airway reflux, Havemann and colleagues<sup>6</sup> examined the possible bidirectional effect between respiratory and upper gastrointestinal tract physiology. A reasonable hypothesis is that a vicious cycle exists between the physical effects of asthmatic airway obstruction and the irritant effects of reflux material on the respiratory mucosa, but although such a cycle is suspected, it is not yet known which comes first.

Hydrochloric acid might be the most harmful component of reflux material, but reflux content can also be non-acidic (pH >4) and can be solid, liquid, gaseous, or mixed. Results of studies in which oesophageal impedance pH monitoring was used to investigate the coexistence of airway reflux symptoms with episodes of reflux showed that, rather than being mainly due to acid, airway reflux was linked to gaseous non-acid components.<sup>7</sup> Two axioms developed from this finding: first, that standard gastro-oesophageal reflux treatment with proton-pump inhibitors might not be effective, and second, that a pH meter was not a reliable test for airway reflux diagnosis because it detects only acid reflux episodes.

Pepsin—unlike acid or bile—is present in all reflux and can directly damage the mucosa, and there has been a growing interest in pepsin, measurable in saliva and bronchoalveolar lavage, as a marker of airway reflux. Hayat and colleagues<sup>8</sup> showed that detection of postprandial salivary pepsin via Peptest (RDBiomed, Cottingham, UK), which uses monoclonal human pepsin antibodies, in concentrations of more than 210 ng/mL had a specificity of 98.2% for diagnosing airway reflux.

The most substantial effect of reflux on the airways occurs immediately above the oesophagus, in the laryngopharynx. In a review on the treatment of airway reflux,<sup>9</sup> gastroenterologists criticised the excessive expenditure on proton-pump inhibitors in patients with airway reflux symptoms who did not improve with their use, and recommended considering functional laryngeal disorders to explain symptoms of airway reflux, which include chronic cough, aphonia, dyspnoea (predominantly inspiratory), and globus pharyngeus (feeling of phlegm or a lump in the throat) and repeated throat clearing.<sup>9</sup>

The larynx has multiple functions—phonation, coughing, and breathing—and laryngeal dysfunction is central to laryngeal hyper-responsiveness. This condition can manifest as laryngopharyngeal paraesthesia, excessive cough, glottal closure in response to mild stimuli such as talking or inhaling strong fragrances, and paradoxical vocal cord movement—ie, adduction of the cords during inspiration. Additional symptoms can include dyspnoea, altered voice, and difficulty swallowing.



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The symptoms from the passage of gastric material to the airways can only be explained by taking a global view of the process as a disease of the vagus nerve, which innervates both the respiratory and gastrointestinal systems. An example that supports vagal damage is the aetiology of chronic refractory cough: the primary abnormality is a change in the cough threshold caused by inflammation of the vagal nerve endings, mainly in the larynx, by reflux material or viral infections. Once the sensitive vagal pathway has been chronically damaged, the cough reflex arc veers towards hypersensitivity, and cough is triggered by trivial stimuli, such as talking, laughing, or sniffing perfumes.<sup>10</sup>

A study by Phua and colleagues<sup>11</sup> shed more light on this complex problem and showed that in patients with gastro-oesophageal reflux and laryngeal involvement, the laryngeal mechanosensitivity threshold was abnormally high, making aspiration more likely, whereas the chemosensitivity threshold was abnormally low, making the acid or pepsin in gastro-oesophageal reflux more likely to trigger cough. This combination of laryngeal dysfunction and airway reflux causes two types of airway problem: aspiration and chronic cough; and chronic or acute dyspnoea, predominantly during inspiration and corresponding to laryngospasm and paradoxical vocal cord movement.

Airway reflux can also be induced by diseases involving chronic airflow obstruction (chronic obstructive pulmonary disorder [COPD], chronic asthma, chronic sinusitis, or paradoxical vocal cord movement). The physical processes inherent to obstructive airway disease predispose to low closing pressures of the upper and lower stomach sphincters, enabling reflux material to reach the upper airway. These findings have been substantiated recently by Burke and colleagues<sup>12</sup> who used high-resolution oesophageal manometry to show an increased inspiratory gastro-oesophageal pressure gradient due to significantly lower intra-oesophageal pressure on inspiration and reduced oesophageal motility in patients with respiratory symptoms than in those without.

In summary, although airway reflux appears to be a predisposing or exacerbating factor for upper and lower airway disease, growing evidence also suggests that obstructive airway disease might be a risk factor for gastro-oesophageal reflux. Numerous findings reinforce the presumed inflammatory role of reflux material in the

airways, yet the symptoms, generally localised to the upper airway, are often missed when investigating a patient with chronic cough, COPD, asthma, or chronic sinusitis. Furthermore, little attention is paid to the consequences of airway reflux, which could partly explain the repeated acute exacerbations of COPD in patients who stopped smoking many years ago—particularly from aspiration of content that carries gastrointestinal microorganisms.

One important reason for the uncertainty about the link between airway reflux and respiratory disease is that the specialty of aerodigestive medicine, proposed by Koufman,<sup>13</sup> and based on the coexistence of symptoms in the two systems, is not yet fully established. This specialty could bring together the research efforts required to explain the association between airway reflux and numerous respiratory problems: cause or effect or mutual dependency?

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