



## Review Article

# Relationship Between Gastro-Oesophageal Reflux and Airway Diseases: The Airway Reflux Paradigm

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### ABSTRACT

Our understanding of the relationship between gastro-oesophageal reflux and respiratory disease has recently undergone important changes. The previous paradigm of airway reflux as synonymous with the classic gastro-oesophageal reflux disease (GORD) causing heartburn has been overturned. Numerous epidemiological studies have shown a highly significant association of the acid, liquid, and gaseous reflux of GORD with conditions such as laryngeal diseases, chronic rhinosinusitis, treatment resistant asthma, COPD and even idiopathic pulmonary fibrosis. However, it has become clear from studies on cough hypersensitivity syndrome that much reflux of importance in the airways has been missed, since it is either non- or weakly acid and gaseous in composition. The evidence for such a relationship relies on the clinical history pointing to symptom associations with known precipitants of reflux. The tools for the diagnosis of extra-oesophageal reflux, in contrast to the oesophageal reflux of GORD, lack sensitivity and reproducibility. Unfortunately, methodology for detecting such reflux is only just becoming available and much additional work is required to properly delineate its role.

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## La relación entre el reflujo gastroesofágico y las enfermedades de la vía aérea: el paradigma del reflujo a vía aérea

### RESUMEN

Nuestro conocimiento sobre la relación entre el reflujo gastroesofágico (RGE) y las enfermedades respiratorias ha conllevado recientemente a cambios importantes. El paradigma previo del reflujo a vía aérea (RVA) o RGE que llega hasta la vía aérea como sinónimo de la enfermedad por reflujo gastroesofágico clásica (ERGE) con la pirosis como síntoma imprescindible ha sido definitivamente rechazado. Numerosos estudios epidemiológicos han mostrado una asociación altamente significativa entre el reflujo ácido, líquido y gaseoso de la ERGE con condiciones tales como enfermedades laríngeas, rinosinusitis crónica, asma resistente al tratamiento, EPOC e inclusive fibrosis pulmonar idiopática. Hoy se sabe que gracias a estudios del síndrome de hipersensibilidad tusígena gran parte del reflujo que llega a la vía aérea no es diagnosticado debido a su escaso o nulo contenido de ácido o a su composición gaseosa. La evidencia para esta relación se basa en la historia clínica que señala una asociación sintomática con factores precipitantes conocidos del reflujo. Las exploraciones para el diagnóstico del RA no poseen la sensibilidad o la reproducibilidad que han demostrado las del reflujo esofágico de la ERGE. Desafortunadamente, el acceso a la metodología para la detección de tal reflujo empezó a ser posible hace muy poco tiempo y se requiere aún muchos trabajos de investigación para perfilar correctamente su papel.

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### Introduction

Recent advances in the comprehension of the physiopathology of gastro-oesophageal reflux (GOR) have created new perspectives in the relationship between GOR and respiratory diseases. To date, there are three areas of attention in the relationship between GOR

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and the upper and lower airway. First, the unique evolutionary development of the human aerodigestive tract makes us prone to GOR. Second, the composition of the reflux material; not just acid or liquid, but also non-acid or gaseous with the additional presence of pepsin and bile salts. And, third, the histological damage that the reflux material causes in the delicate respiratory epithelium. As a consequence, a series of clinical manifestations develops, related with the inflammatory effects on the upper and lower airway.

In this review article, we present a general vision of the trajectory that gastric reflux follows from the stomach to the lower airway. To describe this phenomenon, we prefer the simple term: airway reflux (AR). GOR is the passage of the gastric content towards the oesophagus. The gastric content can continue to reflux along the entire oesophagus until the laryngopharynx, causing laryngopharyngeal reflux (LPR). The term extra-oesophageal reflux is awkward because it includes the entire anatomical area above the esophagus.<sup>1</sup> From the pharynx, the reflux can reach the oral cavity, nasal cavity, the paranasal sinuses or even the middle ear.<sup>2</sup> When the refluxed material passes through the larynx to the lower airway, what happens is what we call aspiration. The detection of pepsin and bile acid using enzyme testing in the material obtained from the bronchoalveolar lavage (BAL) has permitted an objective confirmation of lung aspiration associated with GOR.<sup>3-5</sup>

## Epidemiology

Numerous epidemiological studies have described the association between GOR and respiratory diseases. The RHINE workgroup showed an independent relationship between obesity, nocturnal GOR and habitual snoring, with the start of asthma and respiratory symptoms in adults.<sup>6</sup> El-Serag et al. compared the occurrence of sinusitis and larynx and pulmonary diseases in 101,366 patients with and without esophagitis due to reflux. They showed that erosive esophagitis and oesophageal stenosis were associated with sinusitis, pharyngitis, aphonia, laryngitis, laryngeal stenosis, chronic bronchitis, asthma, COPD, pulmonary fibrosis, bronchiectasis, pulmonary collapse and pneumonia.<sup>7</sup> In a study on more than 4,000 healthy subjects in Yorkshire,<sup>8</sup> the association between chronic cough and gastrointestinal diseases was researched by means of a questionnaire that gave evidence of a relationship between chronic cough, regurgitation and irritable bowel syndrome. Rhul CE et al.<sup>9</sup> demonstrated, in a group of 6,928 participants, that a history of hiatal hernia or esophagitis due to reflux significantly increased the risk of respiratory disease associated with hospitalization. The *Nord-Trondelag Health Survey*<sup>10</sup> included more than 58,000 individuals and showed that acid reflux symptoms frequently coexist with asthma and other respiratory symptoms, regardless of anti-asthmatic medications. Finally, the European ProGERD study, which included 6,215 patients with pyrosis demonstrated a prevalence of extra-oesophageal symptoms of 32.8%.<sup>11</sup> There are two key questions: whether these associations are causal or coincident, and whether the GORD paradigm, exclusively with acid reflux and without considering other types of reflux, underestimates the true relationship.

## Physiopathology

### ¿Why Airway Reflux?

We humans are prone to reflux and aspiration because we have a unique evolutionary development. We are the only mammals that are truly bipeds. In all the other vertebrates, there is a right angle between the oesophagus, which is found situated along the posterior part of the thorax and crosses the diaphragm, and the stomach,

which is in a vertical position. This anatomy minimizes any tendency towards reflux during the aperture of the lower oesophageal sphincter (LOS). In contrast, the human oesophagus descends directly towards the stomach, going from the area of low pressure in the thorax to an area of higher pressure in the abdominal cavity. Here the opening of the LOS immediately predisposes reflux episodes. In fact, the crural diaphragm pulls the LOS backwards to the point that it forms a structure in the shape of a J, similar to the anatomy of other mammals. As a consequence, diaphragmatic activation, such as during phonation, precipitates reflux. The physical disruption of this relationship, as in the case of a hernia hiatal, can produce untreatable reflux.

The second important consequence of our evolution is the ability to speak, which is produced thanks to the descent of the larynx during early infancy. This interrupts the laryngeal sphincter mechanism by moving the soft palate away from the arytenoid cartilage and the epiglottis. Unfortunately, this modified anatomy is particularly ineffective in preventing reflux aspiration and can predispose us to a series of respiratory complications related with reflux.<sup>12</sup>

There are three potential mechanisms for the presence of extra-oesophageal symptoms associated with reflux:

- 1) Direct irritation of the airway epithelium by the reflux material;
- 2) Afferent cough reflex hypersensitivity of the airway due to acid reflux;
- 3) A neural reflex between the oesophagus and the air tract.<sup>13,14</sup> Up to fifty episodes of reflux from the stomach to the oesophagus are within the physiological limits of normal, but just one event of reflux that reaches the laryngopharynx could be enough to produce symptoms in the upper airway.<sup>15</sup> Two factors influencing the physiopathology of GOR are the insufficiency of the anti-reflux barrier as well as the diminished mechanisms for oesophageal clearance. The excess in transitory LOS relaxation (TLOSR) as well as the insufficiency to maintain sufficient pressure at the level of the LOS (hypotonic LOS) are accepted mechanisms on which the insufficiency of the anti-reflux barrier are based. The presence of a hernia hiatal, a condition in which a portion of the stomach herniates towards the thorax, facilitates oesophageal reflux during TLOSR much more than in the situation in which the gastro-oesophageal sphincter is found in its normal anatomical situation. Recent findings demonstrate that TLOSR are the main mechanism of distal reflux events, but hypotonic LOS can be more important in proximal reflux events.<sup>16</sup> A greater quantity of acid reflux during TLOSR could contribute greatly to the genesis of air reflux, more than the frequency of TLOSR alone.<sup>17</sup> However, acid reflux does not seem to play an important role in the determination of the response of the upper oesophageal sphincter (UOS) to TLOSR. It has yet to be determined whether patients with predominantly oesophageal symptoms exhibit an exaggerated relaxation of the upper oesophageal sphincter during reflux or if the relaxation is transitory.<sup>18</sup> The degree of aperture of the oesophageal-gastric union could be a key factor in reflux with pH < 4, more than the simple relaxation of the LOS, but this phenomenon has only been recently revealed by means of high resolution manometry.<sup>19</sup>

Oesophageal acid clearance time is the time necessary in order for the oesophageal medium to return to a neutral pH after an episode of acid reflux. Postma et al.<sup>15</sup> showed that patients with airway reflux had a significantly longer clearance time than a control group. The laryngopharynx lacks the oesophageal peristaltic movement and these patients could have increased oesophageal dysmotility, causing

the reflux material to maintain for more time and produce prolonged irritation.<sup>1</sup> Manometric studies of oesophageal peristalsis in patients with laryngopharyngeal reflux revealed abnormal oesophageal motility in 75% of subjects.<sup>20</sup> Kastelik et al. studied patients with chronic cough and showed a high prevalence of abnormal oesophageal manometry with 32% of patients that had exclusive manometric alterations and normal pH studies, inferring that the acid might not be a necessary prerequisite for reflux with respiratory effects.<sup>21</sup>

#### *Composition of Airway Reflux*

Recent observations indicate that there are different compositions of airway reflux. Previously, GORD has been closely associated with acid reflux, but even in this case bile has been implied. Balaji et al. were the first in trying to analyze the characteristics of reflux during a period of 24 hours in healthy ambulatory subjects, using multichannel intraluminal impedance technology. The nature of the reflux was exclusively liquid in 51% and mixed with gas in the remaining 49%. The liquid reflux reaches the middle and proximal oesophagus in 69% of episodes, while gaseous reflux does so in up to 92%. More than half of reflux events are not detected by means of pH studies.<sup>22</sup> Kawamura et al. showed that the episodes of gaseous reflux that is poor in acid are apparently more common in patients with dyspepsia and laryngitis due to reflux when compared with patients with GORD and control subjects.<sup>23</sup> Oh et al. evaluated the impact of the composition of reflux on mucosa damage and oesophageal function using monitoring by means of pH-bilitec. They found that the mixed exposure to acid and bile was present in more than 50% of patients, which was associated with the most severe mucosal lesions and with a greater deterioration in oesophageal function.<sup>24</sup> Recently, Sifrim et al. evaluated the effect of oesophageal perfusions with high and low acid solution on the oesophageal mucosa that is "exposed" and "unexposed", giving evidence that the oesophageal mucosal perfusion with low-acid solutions caused changes identical to those observed after a perfusion with more acid solutions; on the other hand, the distal oesophageal perfusions not only caused changes in the exposed mucosa but also in the more proximal unexposed mucosa.<sup>25</sup> Mild acid reflux above the levels of the upper oesophageal sphincter is deleterious with evidence of cell damage and pepsin activity. In this area there is a lower tissue resistance to pepsin and acid, together with a depletion of laryngeal defences in response to the reflux, such as carbonic anhydrase III.<sup>26</sup> Recently Johnston et al. have demonstrated that pepsin is captured by the laryngeal epithelial cells even in non-acid reflux. These findings could explain why many patients have symptoms and inflammation associated with non-acid reflux and could have important implications for the development of new therapies for airway reflux, such as pepsin receptor antagonists and/or pepsin activity inhibitors.<sup>27</sup>

#### *Respiratory Disease and Airway Reflux*

Cough can originate within the territory of the vagus nerve. Whether GOR is the primary mechanism in patients with chronic cough or is a mere aggravating factor that contributes to an abnormally-high cough reflex is open for debate. The presence of micro-aspirations have been demonstrated in a number of patients with reflux and a variety of pulmonary disorders that include chronic cough<sup>28</sup> and it is thought that the mechanism is a loss of the laryngeal mechanosensitivity.<sup>29</sup> The symptom association probability (SAP), meaning the temporary association between a reflux event and a symptom, has been suggested as the most reliable algorithm for establishing the non-random association between GOR and cough.<sup>13</sup> Symptom association studies have demonstrated that non-acid or

mild acid reflux is important in respiratory disease.<sup>30</sup> The majority of the studies monitoring oesophageal impedance have demonstrated the absence of an important increase in reflux events in patients with chronic cough when compared with normal control subjects. However, Patterson et al. suggested that patients with positive SAP on impedance monitoring could have more reflux episodes that surpass the level of the upper oesophageal sphincter than those patients with negative SAP.<sup>31</sup> Inversely, chronic cough caused by changes in the pressure gradient between the abdominal and thoracic cavities during cough could precipitate reflux and lead to a vicious cycle of cough and reflux.<sup>32</sup>

Ferrari et al. studied 29 asthma patients who underwent oesophageal pH monitoring with the measurement of proximal and distal events and provocation tests with inhalation of methacholine and capsaicin. They concluded that the inhibition of gastric acid secretion does not influence bronchial hyperreactivity, but instead increases cough sensitivity and this effect is related with proximal reflux.<sup>33</sup> Wu et al. demonstrated that oesophageal acid stimulation in subjects with chronic cough with mild persistent asthma increased only the cough sensitivity to capsaicin, but did not induce spontaneous cough. They concluded that GOR could increase the cough response when asthmatics receive noxious stimuli in the airway.<sup>34</sup> It has been recently suggested that there is a potential unified connection between asthma, chronic cough and GOR. Patterson et al. showed high levels of tachykinins in the sputum of patients with asthma and cough associated with acid reflux, and they postulated that the respiratory sensory nerves are activated by the acidification of the oesophageal mucosa.<sup>14</sup> Evidently, the excess of tachykinins in the respiratory medium could mediate the contraction of the smooth muscles, glandular mucus secretion, vascular permeability and the recruitment of inflammatory cells in the bronchial tree.<sup>35</sup>

#### *Clinical Manifestations*

Typically, the main symptoms of GORD are the sensation of pyrosis and regurgitation. In contrast, airway reflux symptoms include hoarseness, chronic cough, expectoration, wheezing, stridor, dyspnea, the sensation of a foreign body, clearing of the throat and dysphonia. The Consensus Group of Gastroesophageal Reflux Disease in Montreal in 2006 recognised pyrosis and regurgitation as common symptoms of typical reflux disease. However, they also stated that the manifestations of GORD include oesophageal and extra-oesophageal syndromes. Reflux cough syndrome, reflux laryngitis syndrome and reflux asthma syndrome were designated as among the extra-oesophageal syndromes with an established association with GORD.<sup>36</sup> The physiopathology frequently does not depend on acid; consequently, therapy with proton pump inhibitors can be ineffective. GOR causes GORD as well as AR, although they are two different diseases.

Chronic cough and laryngeal symptoms are the most common manifestations of AR and, while some of these patients also present pyrosis and/or regurgitation, more than a third of the patients with GOR experience respiratory manifestations exclusively.<sup>37</sup> Out of the 185 consecutive patients consulting at the Chronic Cough Clinic at the University of Hull with a diagnosis of chronic cough, 30% did not present pyrosis due to acid regurgitation in the preceding month. Irwin et al. have suggested that when GOR produces cough, there may be an absence of digestive symptoms in up to 75% of occasions.<sup>38</sup>

The Pro-GERD study included 6,215 patients that were followed-up for two years. It found that the patients with persistent respiratory symptoms had significantly higher scores on the GORD questionnaire.<sup>37</sup> The support to the premise that chronic cough, chronic laryngitis or

asthma due to reflux are multifactorial processes, with reflux as a possible aggravating factor, comes from therapeutic assays where these entities improved with reflux disease treatment.<sup>39-42</sup> The frequent coexistence of chronic cough and GORD is well established. However, to assure an association between cause and effect is more difficult for many reasons, including the simultaneous occurrence of the two entities, the problems with the different definitions of GORD, the limitations of the equipment and the lack of randomised controlled assays. Given these difficulties, it is no surprise that there is a disparity of opinions between the guidelines of respiratory and gastroenterological societies regarding the nexus between GORD and chronic cough. SEPAR, in its guidelines on chronic cough, mentions that the parameter of greatest clinical utility for the diagnosis of cough associated with GOR is monitoring oesophageal pH. It also recommends diagnosing a therapeutic trial with high doses of proton pump inhibitors (PPI) in patients with typical or atypical GOR symptoms.<sup>43</sup>

The recent Yorkshire survey gave evidence that patients with chronic cough had a strong association with gastrointestinal pathology.<sup>8</sup> The highest degree of association was observed with regurgitation more than with pyrosis, suggesting that non-acid reflux is a more important etiological factor in chronic cough than acid reflux.

In standard clinical practice, the wide range of AR symptoms is frequently not well characterised, partially because the symptoms are not described in the medical history or due to the lack of use of appropriate questionnaires.<sup>44,45</sup> If an adequate questionnaire is used in patients, the majority of them can be diagnosed exclusively based on respiratory symptoms such as dysphonia, clearing of the throat, excessive laryngeal mucus, sensation of a foreign body in the throat and cough. In a study including 47 patients with chronic cough and confirmed GOR, Everett et al. demonstrated that classic pyrosis or indigestion were only present in 63% of the patients. The cough that accompanied phonation or rising from decubitus position and was associated with the period after meals or after eating certain foods, clearing of the throat, dysphonia, dysphagia and the sensation of a foreign body in the throat, make up a complex of symptoms that is characteristic of cough due to reflux.<sup>46</sup> The same study showed that the symptoms of chronic cough can be divided into precipitants of cough that affect the lower oesophageal sphincter, such as posture and phonation, factors that cause a transitory opening of the lower oesophageal sphincter, such as eating and postprandial period, and factors that indicate the extra-oesophageal deposition of the reflux, such as a change in the quality of the voice and postnasal drip.

The perception of the episodes of reflux is quite complicated. An important factor is the level of neuronal sensitivity of the respiratory tract. Bredenoord et al.<sup>47</sup> researched the characteristics of reflux episodes in patients with a positive symptom-association probability with physiological acid exposure and they found a greater proportion of reflux episodes that reached the proximal oesophagus. Zerbib et al. evaluated the determinants of the perception of reflux in patients receiving treatment with proton pump inhibitors (PPI) who presented with typical gastroesophageal reflux symptoms (pyrosis and/or regurgitation) in spite of a double dose of PPI. The high proximal extension of the reflux is the only factor associated with the perception of reflux in patients with double doses of PPI. However, in comparison with regurgitation, composition of the reflux, sensitisation of the oesophagus after the acid exposure and delayed clearance of the food bolus seem to play a role in the perception of pyrosis.<sup>48</sup>

Some patients with airway reflux, who do not respond to pharmacological therapy, present regurgitation but from the proximal oesophagus, not from the stomach. Symptoms of oesophagopharyngeal

reflux are similar to the other respiratory manifestations of GOR and seem to exist due to the alteration in the clearance volume and oesophageal dysmotility, but there is no acid or peptic lesion. Acid reflux disease (laryngopharyngeal reflux or gastroesophageal reflux) had been previously diagnosed in 85% of these patients and had been treated without success with proton pump inhibitors and/or with anti-reflux surgery, and 15% had fluoroscopic oropharyngeal anomalies. All the patients presented oesophageal fluoroscopic alterations.<sup>49</sup>

## Diagnostic Tests

Many patients have normal macroscopic endoscopic findings; therefore, the sum of a precise clinical history for AR and a positive therapeutic response are the pillars of its diagnosis. A prolonged therapeutic test with PPI at high doses was considered a first-line diagnostic test in those patients with the suspicion for extra-oesophageal symptoms related with reflux based on studies monitoring pH with PPI in refractory cases.<sup>2</sup> However, there is no evidence in controlled assays and the non-controlled studies show results with confusing data due to the placebo response. In addition, the diagnostic value of a therapeutic test with PPI has been poor even in patients with classic symptoms of GORD,<sup>50</sup> while prolonged studies are not reliable due to the occurrence of spontaneous remission.

A meta-analysis concluded that the acid exposure time at the level of the upper oesophageal sphincter reliably distinguishes LPR patients from normal control subjects.<sup>51</sup> The use of the combination of a laryngoscopic exam and a 24-hour ambulatory pH test can increase the ability to identify patients with LPR, although these tests are not specific.<sup>52,53</sup> The monitoring of oesophageal pH alone does not detect all the GOR events, particularly when the reflux material has little or no acid. For example, two recent studies showed that regurgitation and cough are symptoms more frequently associated with non-acid gaseous gastroesophageal reflux.<sup>54,55</sup> Other methodologies have evolved to complement ambulatory pH monitoring for detecting and characterizing GOR. Intraluminal electrical impedance studies offer the potential to detect and monitor the movement of liquid or air within the oesophagus.<sup>56</sup> The combination of the impedance and pH monitoring techniques is better than the use of either of them alone.<sup>25</sup> The term "weakly acid reflux" is used to describe reflux episodes in which the pH nadir is situated between 4 and 7, and a pH of 7 is the cut-value for a "weakly alkaline reflux" (in other words, non-acid reflux). In fact, the majority of reflux episodes are constituted by weakly acid reflux. Moreover, impedance technology in healthy volunteers show that more than half of GOR events are not detected with pH studies and that liquid reflux reaches the middle and proximal oesophagus in 69% of events, while the gas (or more correctly fumes or vapour) almost always does so.<sup>22</sup> Tutuian et al.<sup>54,57</sup> showed that the majority of reflux episodes in patients that follow an acid suppressor treatment are asymptomatic, and that reflux episodes that extend proximally and have a mixed liquid-gaseous composition are significantly associated with symptoms, with no importance as to whether pH is acid (< 4) or non-acid ( $\geq 4$ ). Another recent analysis of persistent symptoms in patients with acid suppressant treatment detected by means of pH monitoring by impedance showed that the pharyngeal clearance or "clearing of the throat", a typical characteristic of laryngopharyngeal reflux, was the most common symptom.<sup>58</sup>

Nevertheless, the problem of the objective diagnosis of AR persists. Studies by Wo et al.<sup>59</sup> and Cool<sup>60</sup> suggest that there is no convincing evidence that proximal oesophageal monitoring of pH predicts the response to acid suppressant therapy in patients with

symptoms of LPR because monitoring can only measure liquid acid reflux. This has driven several investigators to monitor the pharynx. The original methods for measuring pharyngeal pH were not quite right due to technical problems, such as the drying out of the catheter and the accumulation of mucus and food. The Dx-pH measuring system (Dx-pH; Restech Corporation, San Diego, CA) is a highly sensitive and minimally-invasive device for detecting acid reflux in the posterior pharynx.<sup>61</sup> This sensor detects aerosolised or liquid acid, resists drying out and its electrical continuity is not impeded by the contact of liquids or tissues. Ayazi S et al. have shown the characteristics of mean pH in the oropharynx of healthy subjects using the Dx-pH catheter. The pharyngeal pH score (RYAN) for abnormal pH (limit of 5.5 for standing and 5.0 in supine position) has been calculated in a way similar to the DeMeester oesophageal score.<sup>62</sup> Furthermore, an alternative scoring system has been developed based on the changes in pH. Wiener et al.<sup>1</sup> compared traditional 24-hour pharyngo-oesophageal monitoring with Dx-pH monitoring in 15 patients with extra-oesophageal symptoms. All the events measured with the Dx-pH method were preceded by and associated with falls in distal oesophageal pH in a progressive anterograde manner. However, oropharyngeal studies with the Dx-pH catheter showed a growing pH gradient from the distal oesophagus to the oropharynx. The oropharynx usually presents a mildly acidic pH, rarely with a pH less than 4. This could help explain why the previous attempts at distinguishing normal subjects from the subgroup of patients with atypical symptoms using quantitative cut-values of pH < 4 have not been reliable.

Recently, other objective LPR markers have been developed, such as the detection of pepsin in clinical samples of the upper or lower airway. Knight et al.<sup>63</sup> demonstrated that the immunoassay of pepsin in saliva had a sensitivity of 100% and a specificity of 89% for the diagnosis of LPR.

## Treatment

The extra-oesophageal manifestations of reflux are generally treated with the combination of dietary hygiene advice (changes in diet and behaviour modification) and pharmacological therapy. Recent data confirm that obesity is a well-established risk factor for GOR.<sup>64</sup> Food and drink that contain caffeine should be avoided due to its activity on the oesophageal sphincters. Carbonated drinks produce gastric distension, a powerful stimulus for the onset of TLOS. On the other hand, the consumption of acid drink can reactivate pepsin when the reflux is mildly acid. Nicotine stimulates acid production and precipitates TLOS, therefore smoking should be avoided. Eating smaller meals throughout the day instead of larger portions is also recommended. Some patients may also benefit from raising the head of the bed in order to prevent night-time reflux of gastric content.

PPI therapy is considered the fundamental pillar in the pharmacological treatment in the entire spectrum of GOR. Chang et al. examined the Cochrane database of patients with cough related with GOR<sup>65</sup> and concluded that more randomised, control and parallel-designed studies are needed. Assays of empirical treatments with PPI, as suggested by the guidelines of the *American College of Chest Physicians (ACCP)* and the *British Thoracic Society (BTS)*,<sup>66,67</sup> should be restricted to those patients with significant dyspepsia. The response of other airway symptoms to antacid therapy oscillates between 60 and 98% in uncontrolled studies,<sup>68,69</sup> results similar to those found in chronic cough. Patients with suspicion of AR that do not respond to acid suppression treatment are usually sent to other departments for further diagnostic studies. Esophagogastroduodenoscopy has a very low sensitivity in patients with cough due to reflux.<sup>70</sup>

In asthma patients, 24-hour pH monitoring has shown that up to 80% present abnormal acid reflux.<sup>71</sup> The *Asthma Clinical Research Centers* group of the *American Lung Association* studied asthma patients with poor symptomatic control who were already receiving treatment with inhaled corticoids and did not present the typical symptoms associated with reflux. They found no improvement in the control of asthma after adding a dose of esomeprazole every 12 hours for 6 months. In this randomised, double-blind, controlled study, the patients underwent 24-hour ambulatory pH monitoring before initiating treatment. Approximately 40% of the patients suffered abnormal acid reflux; they did not, however, present a tendency to respond better to PPI therapy than patients with normal pH monitor results.<sup>72</sup> The authors mistakenly concluded that reflux was not a significant problem in difficult-to-control asthma, when in reality their data only support the idea that acid reflux is not important. The current guidelines suggest that a therapeutic trial with PPI is valid; however, these results do not demonstrate improvement in the asthma symptoms.<sup>73</sup> A similar situation occurs in laryngitis due to reflux. Qadeer et al. and Vaezi et al. found that there were no significant differences in the resolution of symptoms or laryngeal signs of laryngopharyngeal reflux between those patients that received treatment with PPI or those who received placebo.<sup>74,75</sup> However, in both cases, in asthma as well as in laryngitis due to reflux, there are three physiopathological facts that have not been considered:

- 1) The effect of pepsin and other proinflammatory mediators on the epithelium in non-acid reflux<sup>27</sup>;
- 2) The oesophageal distension and the stimulation of neuronal inflammation that is not mitigated by PPI<sup>76</sup>;
- 3) The ineffective oesophageal motility as part of the oesophageal reflux refractory to the treatment due to the presence of nocturnal gastric acid.<sup>77</sup>

LOS plays a crucial role in maintaining the mechanical barrier necessary for the prevention of GOR. TLOS has been recognised as the fundamental base mechanism of GOR, and can represent an important therapeutic objective. Preclinical studies have identified several objectives for the pharmacological modification of TLOS. The inhibition of the occurrence of TLOS and GOR mediated by atropine could be related with a central cholinergic block.<sup>78</sup> Blackshaw investigated various aspects of TLOS in ferrets and determined that the vagal gastric mechanoreceptors are an optimal objective for pharmacological therapeutic intervention. Its response to distension is potentially inhibited by the antagonists of gamma-aminobutyric acid (GABA) type B receptors and antagonists of the type 5 metabotropic glutamate receptors (mGluR5). These effects inhibit the occurrence of TLOS and reflux in animal and human models. Clinical studies indicate that both types of medicines could have a potential application in the treatment of GOR.<sup>79</sup> Baclofen, a typical GABA antagonist, inhibits the frequency of TLOS in more than 50%.<sup>80</sup> The greatest problem with baclofen is the limitation of its use in clinical practice due to the poor tolerance of its side effects. Lesogaberan is a potent agonist of GABA (B). *In vitro*, it is captured by the GABA receptors (B), maintaining low extracellular levels in the central nervous system, thus avoiding neurological side effects. In clinical assays of phases I and IIa, treatment with lesogaberan has been well tolerated and has resulted in a substantial reduction in reflux episodes due to the reduction of TLOS.<sup>81</sup>

Metoclopramide and domperidone are dopaminergic antagonists that have also been used as prokinetic agents for gastrointestinal dysmotility. Poe and Kallay discovered in 214 patients with chronic cough that 56 had cough related with GOR. Twenty-four of the 56

patients responded to monotherapy with PPI. Eighteen of the remaining patients improved with the addition of metoclopramide or cisapride.<sup>82</sup> With the emergence of cisapride on the American market in the year 2000, it was necessary to use metoclopramide, bethanechol or erythromycin in prokinetic therapy for the treatment of gastroesophageal reflux. Sifrim et al. studied the effects of azithromycin (group of macrolide antibiotics) on gastroesophageal reflux and observed that it reduced the acid oesophageal content and the exposure volume as well as the number of proximal reflux events in patients with lung transplants.<sup>83</sup> In addition, azithromycin reduces the concentration of bile acids found in the bronchoalveolar lavage of these patients, thus suggesting that GOR and the risk for aspiration are reduced with azithromycin.<sup>84</sup>

Persistent non-acid reflux and aspiration can lead to inflammation of the lower airway and bronchospasm. Anti-reflux endoscopic or surgical procedures provide a mechanical barrier to all types of reflux: acid, non-acid or gaseous.<sup>85</sup> The effectiveness of fundoplication in the treatment of classic reflux symptoms is well-documented, but the role of surgery in the relief of oesophageal reflux symptoms is less clear. Two long-term studies of patients that had pyrosis or regurgitation and underwent fundoplication reported an improvement in respiratory symptoms in a percentage of between 65 and 75% of patients.<sup>86,87</sup> Recently, Kaufman et al. analyzed the long-term results after laparoscopic anti-reflux surgery (LARS) for the treatment of respiratory disorders associated with GOR. In their series, 129 patients were evaluated with airway symptoms (cough, hoarseness, wheezing, throat pain and dyspnea) for the evaluation of the indication of LARS due to the inadequate response of their respiratory symptoms to medication in high doses. LARS improved the respiratory symptoms associated with GOR in 70% of patients and pharyngeal pH monitoring identified those patients who would most likely benefit from LARS.<sup>88</sup> The study of pepsin in the airway could help distinguish the aspiration of reflux material from the direct aspiration caused by uncoordinated swallowing.<sup>89</sup>

A systematic review of surgery for extra-oesophageal reflux<sup>90</sup> analyzed 25 studies with a very variable proportion (15-95%) of favourable responses after fundoplication. In our experience of patients in whom fundoplication did not improve respiratory symptoms, we have observed the persistence of gaseous reflux measured with Dx-pH (unpublished data). More extensive multi-centre prospective assays should be carried out to compare the pharmacological and surgical treatments, applying standardised diagnostic criteria for airway reflux in order to better outline the indications for AR surgery.

#### *Reflux in Other Respiratory Diseases*

The aspiration of small quantities of nasopharyngeal content can occur in half of otherwise-healthy adults, as demonstrated by pulmonary gammagraphic studies.<sup>91</sup> In patients with respiratory symptoms of unexplained aetiology, oesophageal manometry and 24-hour pH monitoring will identify a subgroup with clinically-significant aspirations.<sup>92</sup> These patients suffer a pan-oesophageal motor dysfunction that affects the three barriers against aspiration: the lower oesophageal sphincter, the "oesophageal peristaltic pump mechanism" and the upper oesophageal sphincter. Despite there being no specific data along these lines, the patients that suffer advanced lung disease have poorer tolerance for aspiration events than healthy individuals. COPD patients exhibit an altered coordination of the respiratory cycle with swallowing. Altered breathing-swallowing coordination could increase the risk of aspiration in patients with advanced COPD, possibly contributing to

exacerbations.<sup>93</sup> In addition, these patients could also be affected by GORD and present secondary bacterial colonisations.<sup>94</sup>

GOR is common in patients with asthma and COPD. The increased respiratory work as well as the diaphragmatic flattening and an increase in the intra-abdominal pressure and negative intrathoracic pressure could facilitate reflux of gastric content. In addition, theophylline, beta-2 agonists and oral corticosteroids can diminish the tone of the lower oesophageal sphincter and increase the time of oesophageal contact with the acid.<sup>95</sup> A recently published paper analyzing the effect of comorbidities on the control of asthma patients mentions that nasal polyps, bronchi-pulmonary allergic aspergillosis and also GOR were more frequent in the group of poorly-controlled asthma compared with the well-controlled asthma group.<sup>96</sup> As for COPD, Kempainen et al. showed a prevalence of 57% of GOR in 41 patients with COPD who underwent monitoring with 24-hour oesophageal dual pH catheter. Fifteen percent of the patients with GOR had proximal reflux despite having normal distal results with the catheter. Only one-third reported pyrosis and/or regurgitation.<sup>97</sup> Likewise, Casanova et al. described a prevalence of 62% of GOR in patients with severe COPD, although more than half reported no typical reflux symptoms.<sup>98</sup> Non-acid reflux was not evaluated in this study. The treatment of non-acid reflux could result in a significant improvement of COPD symptoms. Eryuksel et al. carried out a study in COPD patients, trying to identify the frequency of LPR and its effect on COPD symptoms while analyzing the results of its treatment. After establishing the treatment, a significant improvement was noted in COPD symptoms, LPR symptoms and in the exploratory findings of the laryngeal test in patients with LPR.<sup>99</sup>

Currently, GOR associated with sleep is underestimated from a clinical point of view.<sup>100</sup> Johnson et al. carried out an assay controlled with placebo using esomeprazole at 40 mg, 20 mg or placebo during 6 weeks in 75 adults with sleep alterations associated with GOR. After 4 weeks, 73% of the patients treated with esomeprazole presented a resolution of their sleep anomalies associated with GOR and with both doses of the drug an improvement was obtained in the quality of sleep, reduction of missed work hours and increase in work productivity.<sup>101</sup> However, another study showed that the compensatory changes in the pressures at the level of the upper oesophageal sphincter and the gastroesophageal union prevent reflux,<sup>102</sup> even despite the decrease in oesophageal pressure during obstructive sleep apnoea (OSA) events. A recent publication has suggested an association between chronic cough and obstructive sleep apnoea syndrome. A certain number of patients improved after initiating treatment for sleep apnoea together with other therapies for chronic cough.<sup>103</sup> The impact of OSA on the occurrence and perpetuation of chronic cough should be evaluated prospectively in future studies.<sup>104</sup>

In a study of 65 patients with idiopathic pulmonary fibrosis (IPF), 83% presented abnormal distal and/or proximal oesophageal acid exposure.<sup>105</sup> The authors also demonstrated that GOR in patients with IPF is frequently clinically silent, because only 47% present the classic symptoms. In addition, the standard dose of PPI may not suppress acid GOR. Other studies are urgently needed to determine if abnormal acid GOR represents an important risk factor for the development or the progression of IPF. In patients with cystic fibrosis, an increase in GOR has been observed as not secondary to cough. Acid GOR is common, but there may also be mildly-acid GOR. A significant percentage of patients with cystic fibrosis have a risk of gastric aspiration.<sup>106</sup>

GOR is strongly associated with the development of bronchiolitis obliterans syndrome (BOS) after primary lung transplantation. The sensitisation to collagen V is associated with reflux and BOS, and it could play an intermediary role in the pathogenesis of BOS. Assays

studying collagen V reactivity are needed to determine the impact of the anti-reflux procedures in patients with lung transplantation and IPF.<sup>107</sup> Recently, an analysis was completed whose objective was to determine if the high levels of pepsin in the bronchoalveolar lavage of subjects submitted to lung transplantation are related with rejection. It was observed that the higher levels of pepsin were present in patients with acute vascular rejection.<sup>3</sup> Up to 50% of patients with lung transplantation develop BOS within the first years after transplantation. A high prevalence of GOR and aspiration of the gastric content have been reported after lung transplantation. Reflux and aspiration have also been implicated in the development of BOS and anti-reflux surgery has been proposed for its prevention and treatment. However, the causal relationship with BOS and the impact of reflux on survival in lung transplantation should be researched in greater detail.

## Conclusions

The displacement of the gastric and duodenal content, from the stomach through the oesophagus to the laryngopharynx and the upper and lower airways, can lead to different clinical entities such as pyrosis, regurgitation, hoarseness, chronic cough, the sensation of a foreign body in the throat, sinusitis, bronchospasm and chronic dyspnoea. The lack of recognition of airway reflux as the clinical entity causing these symptoms continues to be a major problem. The detection of reflux to the airway by means of new techniques, such as the determination of the presence of pepsin in the respiratory secretions of the airway or the existence of more sensitive pharyngeal catheters has opened new perspectives. Research of esophagobronchial neuronal reflexes is a promising area of research given that neurogenic inflammation could explain the mechanism of symptom production whose origin to date is still unknown. Recent studies suggest that GOR plays an important role in chronic cough, but the role of reflux in chronic laryngitis and asthma is less clear and future assays are needed to identify the subgroup of individuals with oesophageal reflux symptoms who could benefit from treatment with PPI, other pharmacological modalities with TLOSR as a target, or anti-reflux surgical treatment.

In humans, the evolutionary anomaly in the aero-digestive tract favours the transit of the gastric and duodenal content out of the stomach. Our unique ability to speak has made us prone to aspiration. Pulmonologists, otorhinolaryngologists and gastroenterologists are becoming more and more conscious of the physiopathological and clinical importance of the forked axis that communicates the stomach and lungs through the laryngopharynx.

## Conflict of Interest

The authors declare having no conflict of interest.

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