Towards better understanding of symptoms associated with disordered esophageal function
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GENERAL INTRODUCTION

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Pathophysiology of gastroesophageal reflux disease: new understanding in a new era.
Thomas V.K. Herregods, Albert J. Bredenoord, André J. P. M. Smout
Neurogastroenterol Motil. 2015;27(9):1202-13

and

Normative values in esophageal high-resolution manometry
Thomas V.K. Herregods, Sabine Roman, Peter J. Kahrilas, André J.P.M. Smout, Albert J. Bredenoord
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GENERAL INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most prevalent chronic diseases, with prevalence estimates up to 27.8% in North America and up to 25.9% in Europe. There is evidence suggesting an increase, particularly in North America and East Asia, since 1995\(^1\). GERD is associated with a large range of symptoms, which can be divided into typical and atypical reflux symptoms. Typical symptoms consist of heartburn and acid regurgitation, while atypical symptoms are more diverse and less specific, consisting of chest pain, chronic cough, hoarseness, globus, dysphagia, and throat irritation\(^2\).

Throughout time our understanding of the pathophysiology of GERD has evolved, with some remarkable back and forth swings from one view to another prompted by the advent of new investigational techniques. Heinrich Quincke first mentioned reflux-induced esophageal ulceration in his description of 3 post-mortem cases in 1879, which was followed by a paper in 1935 by Winkelstein who corroborated the concept of reflux esophagitis\(^3\), but also linked its presence to the symptom heartburn. In 1951, Allison demonstrated the association between esophagitis and hiatus hernia\(^4\). Subsequently, hiatus hernia was regarded as synonymous to GERD until 1972, at which point Cohen et al. found a consistently hypotensive lower esophageal sphincter (LES) in patients with GERD\(^5\). This new knowledge overshadowed hiatus hernia as a pathophysiological factor for quite some time and it was no sooner than in the year 2000 that van Herwaarden et al. demonstrated that a low LES pressure was frequently associated with reflux episodes in hiatus hernia but only rarely in GERD patients without a hiatus hernia\(^5\). Meanwhile, by 1976, Dent and co-workers had developed their sleeve sensor which allowed for continuous LES pressure measurement\(^6\). This technique led to the observation, published in 1980, that 98% of reflux episodes in recumbent subjects were associated with transient (5-30 seconds) episodes of (“inappropriate”) complete LES relaxation (TLESR) instead of being related to a persistently low LES pressure\(^7\). The use of the Dent sleeve further discouraged thinking about hiatus hernia and multiple publications implicating TLESRs as a major role in the etiology of GERD saw the light. Subsequent studies emphasized that TLESRs are the major determinant of reflux in healthy volunteers\(^8\), that they are physiological due to their involvement in belching\(^9\), and that the incidence of TLESRs and the proportion of TLESRs associated with reflux are not higher in GERD patients than in asymptomatic volunteers. However, in GERD patients TLESRs are twice as likely to be associated with acid reflux\(^10\). Subsequently, the development of ambulatory esophageal pH monitoring resulted in recognition of non-erosive reflux disease (NERD), which was followed by the introduction of esophageal impedance monitoring that led to the awareness that reflux of gas and liquid can cause symptoms regardless of acidity\(^11\). It was only by 2006 that the ‘Montreal definition’ of GERD was developed which defined GERD as
‘a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications’

This thesis aims to address current topics in the field of gastroesophageal reflux disease, reflux-related chronic cough, and non-cardiac chest pain and dysphagia. Our investigations were prompted by the impression that there are overlaps and interrelationships between the disorders which would merit further investigation.

**TYPICAL REFLUX SYMPTOMS**

**Pathophysiology**

Reflux of gastric content into the esophagus occurs several times per day in all subjects. Generally, these reflux episodes remain asymptomatic. However, in some individuals reflux of gastric content can result in troublesome symptoms such as heartburn and regurgitation. When mucosal damage in the esophagus has taken place or the symptoms are considered troublesome then one speaks of GERD.

Some factors prevent the occurrence of reflux. The esophagogastric junction (EGJ) functions as an anti-reflux barrier and consists of the smooth muscle of the lower esophageal sphincter (LES) which is surrounded by oblique gastric fibers. These are anchored to the striated muscle of the crural diaphragm by the phreno-esophageal ligament. The overlap between the LES and the crural diaphragm results in a competent anti-reflux barrier. After reflux has entered the esophagus, the main defense mechanisms are mechanical esophageal clearance by peristalsis and chemical clearance in the form of salivary bicarbonate which normalizes the pH.

In patients with GERD some factors promote the occurrence of reflux by disrupting the physiological defense mechanisms, while other factors increase the perception of the refluxed gastric content. Both of these are important pathophysiological mechanisms in GERD. GERD symptoms tend to be common among athletes, with epidemiological data indicating that upper gastrointestinal symptoms occur in up to 58% of surveyed athletes. The mechanisms by which exercise results in reflux are still poorly understood. In chapter 3 of this thesis we investigated the effect of exercise on reflux severity and examined the underlying reflux mechanisms.

**Diagnosis**

Several diagnostic tests can be used to diagnose a patient with GERD. In primary care, the so-called proton pump inhibitor (PPI) test can be used in which it is assessed whether the patient’s symptoms respond well to a trial of acid-suppressive medication (PPIs). It is important to note that this method has a limited sensitivity and specificity. If symptoms persist, patients tend to be referred to a gastroenterologist and then an esophagastroduodenoscopy is often the first investigation performed. This investigation allows to distinguish patients who have macroscopic mucosal damage (reflux esophagitis, usually classified according to the LA classification) or a Barrett’s
esophagus from patients who lack any macroscopic signs of GERD (non-erosive reflux disease (NERD)).

Further investigation can be achieved through the use of pH monitoring\textsuperscript{20}. This investigation allows for the detection of reflux episodes by detecting a drop in pH. However, not all reflux episodes are acidic (pH<4), and as a result the weakly acidic (pH 4-7) or alkaline (pH>7) reflux episodes are not detected. This problem was solved by the introduction of impedance monitoring, as this technique allows for the detection of the movement of both liquid and gas, regardless of the acidity. Furthermore, using 24-hour pH-impedance monitoring one can gather detailed information on each reflux episode, including the pH drop, nadir pH, the proximal extent of the reflux, and the volume and acid clearance times. In \textit{chapter 6 and 7}, we used this technique to determine why some reflux episodes cause symptoms such as cough and non-cardiac chest pain, while others do not.

Using 24-hour pH-impedance monitoring it is possible to differentiate patients with NERD from patients with functional heartburn and other disorders depending on the acid exposure time and the association between reflux symptoms and reflux episodes. It is important to note that a diagnosis of NERD can only be made when, in addition to the absence of abnormalities during upper endoscopy, there is objective evidence that the patients’ symptoms are caused by reflux. This can be achieved by finding a pathological esophageal acid exposure time or by finding a positive association between symptoms and reflux events during a 24-hour measurement. A reflux episode is considered to be associated with a symptom when the symptom occurs within 2 minutes following the onset of the reflux episode. Statistical tests such as the symptom index (SI)\textsuperscript{21} and symptom association probability (SAP)\textsuperscript{22} can then be used to determine whether the relationship occurs more frequently than can be explained by chance. Patients who have a physiological esophageal acid exposure time and a clear association between reflux events and symptoms during the measurement are referred to as hypersensitive esophagus. Patients who lack a relation between symptoms and reflux (no erosions during endoscopy, normal acid exposure, no response to acid suppression and a negative symptom-reflux association) are diagnosed with functional heartburn and therefore do not have GERD. In \textit{chapter 2} of this thesis we use 24-hour pH-impedance monitoring to investigate whether patients with reflux symptoms not responding to PPI have GERD or whether many patients have a functional disorder such as functional heartburn.

Esophageal manometry plays a pivotal role in the diagnosis of esophageal motility disorders. In the work-up of GERD patients the technique provides information on the position of the LES, required for the correct placement of the pH-impedance catheter. In addition, manometry serves to rule out major motility disorders such as achalasia, which can be confused with GERD. In the 1940s, the first clinical application of esophageal manometry began with set-ups of water-filled balloons. Since then the technique has evolved via systems that used either water-perfused or solid-state
catheters with relatively low spatial resolution (now labeled conventional manometry), to systems with closely spaced recording sites, known as high-resolution manometry (HRM)\textsuperscript{23}. Currently, several different HRM systems are commercially available and in addition new types of catheters are being developed as the clinical importance of esophageal manometry grows. The development of HRM systems has led to multiple advantages in comparison to the use of conventional manometry, such as the establishment of an objective measurement of the gastro-esophageal junction (EGJ) relaxation, namely the integrated relaxation pressure (IRP)\textsuperscript{24}, and a more detailed characterization of esophageal body motor response\textsuperscript{25,26}. In chapter 3 we use HRM to evaluate the esophageal motility and EGJ in detail while the patient is running on a treadmill in order to understand more about the pathophysiology of reflux during exercise. In chapter 10 we use HRM to evaluate whether subtle motility problems or abnormalities visualized on HRM could explain dysphagia in a subset of patients with unexplained non-obstructive esophageal dysphagia according to the Chicago classification v3.0\textsuperscript{27}.

**CHRONIC COUGH**

Chronic cough is defined as a cough which persists for more than 8 weeks. It is a common problem estimated to affect 9-33\% of US and European populations\textsuperscript{28}. Besides causes such as post-nasal drip and asthma, GERD is considered to be a significant contributing factor to chronic cough\textsuperscript{29}. As a result, a causal link between GERD and chronic cough is often presumed. Patients are then exposed to high-dose and long-term empirical therapy with proton pump inhibitors (PPIs)\textsuperscript{30}.

In patients with chronic cough, pulmonary and ear, nose and throat examination are advised to rule out other causes. Following this, an upper endoscopy and a 24-hour pH-impedance measurement can take place\textsuperscript{31}. However, a pathological esophageal acid exposure time or the presence of esophagitis or Barrett’s metaplasia do not necessarily prove a causal relationship between reflux and chronic cough\textsuperscript{32}. Similarly, the absence of these abnormalities does not rule out GERD as a causal factor. In order to establish a causal relationship between the occurrence of reflux events and cough bursts, ambulatory 24-hour pH-impedance monitoring in combination with an objective measurement of cough can be used. As mentioned previously, in reflux studies a two-minute time window is used to establish a relationship. In chapter 4 we evaluate whether this two-minute time window can also be used to diagnose patients with reflux-induced cough while in chapter 5 we evaluate the importance of 24-hour ambulatory pH-impedance-pressure monitoring in finding a causal relationship between chronic cough and reflux.

Two different pathophysiological mechanisms have been suggested for reflux-induced cough. The first is that (micro)aspiration of gastric content triggers the cough reflex by irritating the respiratory tract. The second is that refluxate reaching the distal
esophagus can trigger a cough reflex through stimulation of a vagal esophagobronchial reflex\textsuperscript{29}. In chapter 6 we use 24-hour pH-impedance-pressure monitoring to learn more about the mechanism by which reflux induces cough and to understand more about why some reflux episodes in the same patient are associated with cough while others are not.

**CHEST PAIN AND DYSPHAGIA**

Non-cardiac chest pain (NCCP) is defined as recurrent retrosternal chest pain which remains unexplained after a cardiac workup. It is a common disorder with a prevalence of 13\% up to approximately 25\%\textsuperscript{33,34}. NCCP has many causes including GERD, esophageal dysmotility, psychiatric disease such as panic attacks, and musculoskeletal pain\textsuperscript{35}. GERD is considered to be the most common gastrointestinal cause of NCCP\textsuperscript{36}, with many studies showing an association between NCCP and GERD\textsuperscript{34,37}. Therefore, evaluating whether GERD is the cause of the chest pain is an important step in the evaluation of patients with NCCP. Nevertheless, chest pain can also be the result of esophageal dysmotility including distal esophageal spasm and jackhammer esophagus. Similarly to NCCP, dysphagia can also be the result of GERD.

In patients with NCCP or dysphagia, HRM can be performed to evaluate whether esophageal dysmotility is the cause of the complaint. Furthermore, in patients with NCCP, 24-hour pH-impedance monitoring is often carried out to establish whether GERD is the cause of the chest pain. It remains unclear why some reflux episodes in the same patient cause chest pain while others do not. In chapter 7 we evaluate NCCP patients in detail in order to understand more about the mechanism by which reflux causes chest pain. It is also possible to perform 24-hour ambulatory manometry synchronously with 24-hour pH-impedance monitoring. This allows for the evaluation of the temporal association between spasm and the chest pain symptom. However, it is unclear whether this is still beneficial since the introduction of HRM. In chapter 8 we assess the additional yield of ambulatory pressure monitoring to stationary HRM alone in patients with NCCP. The use of HRM has also resulted in the finding of a new condition called jackhammer esophagus in which hypercontractile esophageal contractions are seen. Jackhammer esophagus is known to cause both the symptom chest pain and dysphagia, yet not much is known about this new condition. Therefore, in chapter 9 we evaluate a large cohort of patients with jackhammer esophagus to investigate whether certain manometric findings are associated with the presence of symptoms.

Despite performing the aforementioned tests, a diagnosis for the chest pain and dysphagia is not always found. If, after evaluation for the presence of GERD, eosinophilic esophagitis, or major esophageal motor disorders (achalasia/EGJ outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis) the chest pain remains unexplained, then the patient is considered to have functional
chest pain\textsuperscript{38}. Similarly, if no structural, mucosal, or motor abnormalities can explain the cause of the dysphagia, then patients are diagnosed with functional dysphagia\textsuperscript{38}. In \textbf{chapter 8} we evaluate what proportion of patients with NCCP end up with a diagnosis of functional chest pain, while in \textbf{chapter 10} we evaluate whether subtle forms of dysfunction of the EGJ can explain the dysphagia symptom in a subset of the patients with unexplained non-obstructive esophageal dysphagia according to the Chicago classification v3.0\textsuperscript{27}. 


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