New Techniques to Evaluate Esophageal Function

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Abstract
Classical techniques like videofluoroscopy, stationary manometry and ambulatory 24-hour pH-metry are routinely used in the clinic to study patients with dysphagia, chest pain and reflux-related symptoms. Although many patients can be accurately diagnosed and their therapy successfully guided with these techniques, in many other patients, non-obstructive dysphagia or chest pain cannot be attributed to clear fluoroscopic or manometric abnormalities. Furthermore, ambulatory 24-hour pH-metry often shows a poor association between spontaneous acid reflux events and esophageal or extraesophageal symptoms, particularly in patients ‘on’ treatment. Non-obstructive dysphagia can be assessed with high-resolution manometry to detect segmental disturbances of peristalsis, increase in pressure gradient across the lower esophageal sphincter (LES) or abnormal axial movement of the LES during esophageal spasm. Impedance evaluation of bolus transit is a non-radiological method that can evaluate the functional relevance of manometric abnormalities. Patients with non-cardiac chest pain that do not respond to proton pump inhibitor therapy can be further assessed with intraluminal high-frequency ultrasound to detect sustained esophageal contractions of the longitudinal muscle layer. Impedance planimetry, with multimodal esophageal stimulation, may contribute to evaluate the sensitivity to mechanical, thermal and chemical stimuli. Finally, patients with persistent symptoms of gastroesophageal reflux in spite of adequate treatment with proton pump inhibitors may still have weakly acidic reflux and/or bile reflux associated with their symptoms. These types of refluxates can now be detected with combinations of pH-impedance or pH-Bilitec monitoring. This review will describe the available new techniques to evaluate patients with non-obstructive dysphagia, non-cardiac chest pain and persistent gastroesophageal reflux symptoms.

Introduction
Normal esophageal function allows for food transport and prevents reflux of gastric contents into the esophageal lumen as well as esophageal contents into the airway. Impaired esophageal function may be the cause of symptoms like dysphagia or chest pain or may underlie abnormal gastroesophageal reflux (GER) or delayed clearance of damaging gastric material.

Classical techniques like videofluoroscopy, stationary manometry and ambulatory 24-hour pH-metry are routinely used in the clinic to study patients with dysphagia, chest pain and reflux-related symptoms. Although many patients can be accurately diagnosed and their therapy
successfully guided with these techniques, in many other patients, non-obstructive dysphagia or chest pain cannot be attributed to clear fluoroscopic or manometric abnormalities. Furthermore, ambulatory 24-hour pH-metry often shows a poor association between spontaneous acid reflux events and esophageal or extraesophageal symptoms. This review will describe new methods to evaluate patients with non-obstructive dysphagia, non-cardiac chest pain and GER symptoms.

Non-Obstructive Dysphagia

High-Resolution Manometry
Esophageal peristalsis is a continuum event along the esophageal body and lower esophageal sphincter (LES). The ability of standard manometry with 5–8 recording channels to predict the success or failure of bolus transport is limited by poor spatial resolution. Motor abnormalities that disturb bolus transport can be focal and limited to a short segment of the tubular esophagus and will be missed by pressure sensors placed too far apart [1]. Furthermore, hypotensive pressure waves, limited to a segment as short as 3 cm, can lead to bolus escape. Whether focal abnormalities are functionally or clinically significant has not been assessed.

With high-resolution manometry (HRM) the number of recording sites is increased and pressures are sampled at 1-cm intervals over a 26- to 32-cm segment of the esophagus [2]. Topographic contour plots are derived by aligning pressure data from multiple recording sites on a planar surface and pressure information is displayed using three-dimensional plotting formats. These contour plots reveal that esophageal peristalsis is comprised of a chain of pressure events. Four discrete pressure segments have been identified consistently from the proximal esophagus through the LES that are separated by three pressure troughs. The first segment represents the skeletal muscle component of the esophageal body and extends from just below the upper esophageal sphincter to the first pressure trough. The smooth muscle segment of the esophageal body is then identified by the second and third peristaltic segments that are separated by a second trough. A third pressure trough separates the third segment from the LES aftercontraction (the fourth peristaltic segment), and the chain is completed. The second pressure trough had not been appreciated prior to the use of HRM. Available data suggest that the two smooth muscle segments are under different neuromuscular control and can react separately. The proximal segment is more responsive to cholinergic stimulation, whereas the distal segment probably is more reflective of non-cholinergic control mechanisms in that region [2]. HRM has been compared to conventional manometry. HRM correctly identified all patients with achalasia and was significantly more effective in segregating aperistaltic disorders and incomplete LES relaxation [3]. In a more recent study, the ability to predict the success of bolus transport (assessed with videofluoroscopy) from HRM and conventional manometry was compared. Receiver operating characteristic analysis demonstrated that HRM predicts the presence of abnormal bolus transport more accurately than conventional manometry. Furthermore, HRM identified esophageal motor dysfunctions not detected by conventional manometry and radiography. These included localized disturbances of peristalsis and abnormal movement of the LES during esophageal spasm [4].

HRM and simultaneous videofluoroscopy were used to analyze normal pharyngeal swallows and correlate intraluminal pressures with trans-sphincteric bolus flow. HRM can depict the pharyngo-esophageal segment space-time-pressure structure and specific physiological events related to upper esophageal sphincter opening and trans-sphincteric flow during normal swallowing [5]. With accurate measurements of intrabolus pressure gradient it is possible to identify pathological constriction in the upper esophageal sphincter during flow [6].

HRM can be used to better characterize the function of the LES. For example, it makes possible to clearly distinguish the diaphragmatic pressure component from the LES. Two pressure peaks can be found both in hernia patients and in healthy volunteers [7, 8]. Furthermore, it is at least as accurate as sleeve sensor manometry for the detection of transient lower esophageal sphincter relaxations (TLESRs) [9]. Finally, Staiano and Clouse [10] utilized HRM in patients with achalasia. They reported that using this technique, a trans-sphincteric pressure gradient >5 mm Hg had high sensitivity (94%) and specificity (89%) for achalasia regardless of the presence or absence of peristalsis.

Evaluation of Bolus Transit with Esophageal Impedance
Videofluoroscopic evaluation of barium swallows is the gold standard to evaluate esophageal bolus transit, but unfortunately the radiation used during videofluoroscopy limits the number of swallows that can be examined. Esophageal impedance can be used to evaluate bolus transport without radiation hazards.
Silny et al. [11, 12] first described the technique for measuring intraluminal impedance in 1991. Intraluminal electrical impedance is based on the measurement of electrical impedance between closely arranged electrodes during a bolus passage using an intraluminal probe. Cylindrical shaped metal electrodes are mounted on a thin plastic catheter. Each neighboring pair of electrodes (impedance segment) is connected to an impedance voltage transducer, which delivers a measuring current. The output of the measurement represents the electrical impedance around the catheter in the section between the pair of electrodes. The impedance is inversely proportional to the electrical conductivity of the luminal contents and the cross section area between the two electrodes. Air has a low conductivity and yields an impedance increase, while swallowed or refluxed material has a high conductivity and yields an impedance drop. Furthermore, luminal dilation, i.e., induced by a bolus entry in the measuring segment, results in an impedance drop, whereas luminal narrowing, i.e., during an occlusive contraction, causes an impedance increase [12]. Changes in temporal-spatial patterns in impedance are identified at various levels within the esophagus, allowing differentiation between antegrade (i.e., swallow) and retrograde (i.e., reflux) bolus movement [13, 14].

Animal and human validation studies were performed to assess the sensitivity and accuracy of impedance for reflux detection and intraesophageal bolus movement.

Simultaneous videofluoroscopy and impedance were recorded during barium swallows in healthy human subjects. During barium swallows the fluoroscopic imaging, the impedance recording and a digital timer were simultaneously displayed on a single screen and videotaped for analysis. There was a strong correlation between both methods for the measurement of the time to esophageal filling (r² = 0.89) as well as the time to esophageal emptying (r² = 0.79) [15]. Scintigraphy and impedance were recorded during labeled water swallows (Tc⁹⁹) in another group of healthy subjects. The distal transit time of labeled water, measured with scintigraphy, correlated significantly with the corresponding impedance measurement (r² = 0.92) [16].

Bolus transit patterns, measured by impedance, were compared with barium esophagrams in normal subjects. Impedance and barium swallows showed three bolus transit patterns: normal bolus transit, stasis in the proximal esophagus and retrograde escape of a residue of incompletely cleared bolus from just above the LES. The two methods were in agreement on the pattern type in 97% of swallows [17].

Impedance parameters calculated are (1) total bolus transit time as time elapsed between bolus entry at 20 cm above LES and bolus exit at 5 cm above LES, (2) bolus head advance time as time elapsed between bolus entry at 20 cm above LES and bolus entry at 15, 10, and 5 cm above LES, (3) bolus presence time as time elapsed between bolus entry and bolus exit at each impedance-measuring site (5, 10, 15, and 20 cm above LES), and (4) segmental transit times as time elapsed between bolus entry at a given level above LES and bolus exit at the next lower level. Swallows are classified by impedance as showing: complete bolus transit if bolus entry is seen at the most proximal site (20 cm above LES) and bolus exit points are recorded in all three distal impedance-measuring sites (i.e., 15, 10, and 5 cm above the LES) and incomplete bolus transit if bolus exit is not identified at any one of the three distal impedance-measuring sites [18, 19]. One American study and one Netherlands-Australian cooperative study assessed the relationship of liquid and viscous bolus transit measured by impedance with esophageal contractions measured by manometry in healthy volunteers [18, 19]. Subjects received 10 liquid and 10 viscous materials. Both studies showed that more than 95% of manometrically normal liquid and viscous swallows in healthy subjects had complete bolus transit as measured by impedance. Almost half of manometrically ineffective swallows had complete bolus transit, and many manometric simultaneous sequences had complete bolus transit. Over 93% of normal individuals had at least 80% complete liquid and/or at least 70% complete viscous bolus transit.

A recent study in 350 patients with esophageal symptoms referred to a motility laboratory showed that none of the patients with achalasia and scleroderma had normal bolus transit. Fifty-one percent of patients with ineffective esophageal motility and 55% of patients with DES had normal bolus transit while almost all (>95%) patients with normal esophageal manometry, nutcracker esophagus, poorly relaxing LES, hypertensive LES, and hypotensive LES had normal bolus transit. Abnormal bolus transit was more frequent in patients presenting with dysphagia than with any of the other symptoms. Abnormal liquid bolus transit was identified in 42% of patients presenting for dysphagia, 18% of patients with heartburn, 14% of patients with chest pain, 24% of patients with chronic cough, 11% of patients with regurgitation and hoarseness, and 20% of patients with globus. The study also showed that not all patients with an increased number of low amplitude or simultaneous contractions have impaired bolus transit [32].

New Techniques to Evaluate Esophageal Function
The clinical value of normal bolus transit as measured by impedance is under current investigation in patients with non-obstructive dysphagia and in pre-fundoplication assessment.

Non-Cardiac Chest Pain

Non-cardiac chest pain (NCCP) is defined as ‘angina-like’ chest pain that is not due to ischemic heart disease or other cardiac pathology. Symptoms of chest pain may be present in patients with esophageal motility disorders and GER disease (GERD). Patients with esophageal pain experience symptoms that are nearly indistinguishable from cardiac pain. A number of stimuli may cause esophageal pain. Acid, mechanical distension of the esophagus, osmolality and temperature are some of the noxious stimuli that may elicit heartburn as well as chest pain.

Esophageal motility disorders are identified manometrically in 30% of patients with NCCP. Esophageal spasm and nutcracker esophagus as the cause of ‘angina-like pain’ have been discussed for a long time. The observation that patients may get relief of their esophageal pain with smooth muscle relaxants (nitroglycerine) suggests that smooth muscle contraction may indeed elicit pain. However, these motility disorders as the cause of esophageal pain have not been clearly demonstrated by prolonged ambulatory pressure recordings. Studies failed to find a temporal correlation between pain events and abnormal esophageal contractions in the majority of patients with NCCP. All of these prolonged ambulatory motility studies were done using intraluminal pressure monitoring techniques which records contraction of the circular muscles of the esophagus. Recent studies using esophageal high-frequency intraluminal ultrasound (HFIUS), revealed that longitudinal muscle contraction may be important in the genesis of esophageal pain.

High-Frequency Ultrasound

HFIUS was developed to study intravascular anatomy of the coronary blood vessels [19, 20]. Liu and Miller [21–23] first studied esophageal motility using a HFIUS probes. Unlike manometry, this technique measures the thickness of the esophageal wall and allows calculation of esophageal longitudinal muscle contraction, biomechanics of the esophageal wall and its behavior during hypertrophy or reflux induced distension. The HFIUS imaging may be combined with manometry, pH and impedance measurements.

HFIUS probe catheters are available in different diameters (1–3 mm) and various lengths (95–150 cm). The US frequency of the transducers ranges from 9 to 40 MHz and it provides high-resolution images. The depth of penetration decreases as the transducer frequency increases, whereas image resolution increases. Ultrasound images reveal that the esophagus resembles a ‘slit’ in shape at rest. The muscle is somewhat thicker in the distal esophagus as compared with the proximal esophagus. During contraction, the esophagus assumes almost a geometrically circular shape, which is ‘most likely’ the reason for circumferential symmetry of esophageal pressures. There is a marked increase in the thickness of both circular and longitudinal muscle layers during esophageal contraction. The detailed analysis of the ultrasound images and concurrent pressure recordings reveals a close temporal correlation between the changes in pressure and muscle thickness during contraction [24–26]. Nicosia et al. [27] proved that the thickening of both circular and longitudinal muscle layers observed on US images is the result of longitudinal muscle contraction.

Using HFIUS images, longitudinal muscle contraction has been identified as a possible mechanism of NCCP. Simultaneous recording of the esophageal pH, pressure, and HFIUS images revealed a sustained contraction of the longitudinal muscle of the esophagus (SEC) prior to the onset of pain events. Interestingly, this sustained contraction of the longitudinal muscle was not associated with a sustained increase in esophageal pressure [24].

Temporal correlation alone is no proof of a causal relationship. However, sustained longitudinal muscle contractions and chest pain can be pharmacologically induced simultaneously with edrophonium hydrochloride. Similar to chest pain, prolonged monitoring of the esophagus with HFIUS and manometry revealed a SEC prior to the onset of heartburn. However, the mean duration of SEC associated with spontaneous heartburn events (32 s) differed significantly from the duration of SEC (71 s) associated with chest pain events [25].

Further studies from different centers using HFIUS are required to confirm the relationship between sustained esophageal contractions of the longitudinal muscle and NCCP.

Impedance Planimetry and Multimodal Esophageal Sensory Evaluation

Combined impedance planimetry with manometry allows measurement of cross-sectional area (CSA) and intraluminal pressure at the site of distension simultaneously facilitating calculation of some of the biomechani-
cal properties of the esophageal wall [28, 29]. Three manometry ports positioned at 6, 12, and 18 cm from the catheter tip are used to record pressure above, within, and below a 3-cm-long polyethylene distension bag, within which were housed a manometric channel and two pairs of ring electrodes for impedance measurement. Tension at the site of distension can be calculated using the law of Laplace, which allows the derivation of tension using the formula tension = radius \times pressure, where the radius is calculated from the square root of CSA divided by \pi, and pressure is the transmural pressure recorded from within the distending bag. Stepwise increments in balloon pressure is the transmural pressure recorded from within the distending bag. Stepwise increments in balloon pressure from 5 to 40 cm H\textsubscript{2}O induce an increase in CSA, wall tension and strain. The tension/strain relationship increases exponentially. Balloon distension induces tertiary contractions and secondary peristalsis: graded balloon distension increases esophageal CSA, wall tension, and strain. When a threshold is reached, tertiary contractions and secondary peristalsis develop at pressures less than 50\% of sensory threshold. At higher pressures, chest pain is induced.

Rao et al. [30] showed that in patients with chest pain and normal cardiac and esophageal evaluations, impedance planimetry of the esophagus reproduces pain and is associated with a 50\% lower sensory threshold for pain, a 50\% lower threshold for reactive contractions, and reduced esophageal compliance.

Impedance planimetry was used to measure the CSA during esophageal distension to ascertain the degree of stretch and tension that initiated motor and sensory responses. Hyoscine-N-butyl bromide, a cholinergic muscarinic receptor blocker, was also used to alter esophageal tension during distension. It reduced both esophageal motility and tension during distension without altering the relationship between sensation intensity and CSA, suggesting that esophageal stretch, rather than tension, appears to be the major factor influencing sensory responses to esophageal distension [31].

The sensory and motor responses of the esophagus were studied before and after sensitization of the distal esophagus with acid perfusion in healthy volunteers. The sensitization resulted in allodynia and hyperalgesia to the distention volumes, and the degree of sensitization was related to the infused volume of acid. There was a hyper-reactivity of the esophagus following acid perfusion, with an increased number and force of the phasic contractions, but the muscle tone did not change [32].

A multimodal pain assessment model was developed integrating electrical, mechanical, cold, and warmth stimuli into the same device. Mechanical stimuli were delivered with an impedance planimetric system. Thermal stimuli were performed by circulating water of different temperatures (5–50°C) inside the bag. There are differences between the sensations evoked by the four stimulus modalities, indicating activation of different visceral nerve pathways [32]. There are no sex differences in the assessments of the multimodal stimulations. However, a larger referred pain area in females reflects sex differences in central pain processing [33].

The same technique was used in patients with esophagitis. After preconditioning of the tissue, painful mechanical stimuli were applied as distensions with a bag using an impedance planimetric method. Thermal stimulation was done by re-circulating water at 1 and 60°C in the bag. The area under the temperature curve (AUC) represented the caloric load. The referred pain area (being a proxy for the central pain mechanisms) to the mechanical stimuli was drawn at maximum pain intensities. The patients were not hypersensitive to mechanical stimuli, but the referred pain area was larger and more widespread. In contrast, the patients were hypersensitive to heat stimuli. These data suggest that peripheral sensitization of heat receptors and facilitation of central pain mechanisms may underlie symptoms in patients with esophagitis [34].

### Persistent Symptoms in Patients with GERD ‘on’ Proton Pump Inhibitor

Detection of acid GER, its proximal extent and its relation with GER symptoms has improved significantly during the last years. However, the poor correlation between acid reflux episodes and esophageal or extra-esophageal symptoms observed in many patients, the high prevalence of non-erosive GERD and functional heartburn (not associated with increased esophageal acid exposure) and the persistence of a non-negligible proportion of patients with GERD refractory to adequate proton pump inhibitor (PPI) therapy are still problems to be solved and have prompted to focus attention on less acidic reflux episodes as a possible explanation.

### Impedance-pH Monitoring

Combined impedance-pH monitoring allows detection of all reflux events and distinction between acid, weakly acidic and weakly alkaline reflux. Furthermore, this combined technique allows assessment of duration or proximal extent of a reflux event. A recent consensus
report provided a detailed nomenclature for reflux patterns detected by impedance-pH monitoring [36].

Gastroesophageal liquid reflux is detected as an orally progressing drop in impedance, starting at the level of the LES and propagating to more proximal impedance-measuring segments. Impedance is very sensitive for detection of small volumes of liquid and similar drops in impedance are observed with boluses of 1 and 10 ml [37]. Therefore, so far, the intraluminal impedance technique cannot estimate the volume of the refluxate. GER of gas is detected as an almost simultaneous or rapidly orally progressing rise in esophageal impedance in at least two esophageal impedance channels. In the upright position, intraluminal air is better detected by impedance recordings in the most proximal esophagus. Impedance cannot estimate the volume of air refluxed.

Reflex events are diagnosed by impedance and their acidity is characterized by simultaneous pH-metry [36]: acid reflux is defined as a ‘reflux episode that decreases esophageal pH across 4, or reflux that occurs when esophageal pH is already below 4’.

Reflex episodes when the basal esophageal pH is already below 4 represent a special category of acid reflux, previously described as ‘re-reflux’ and now re-named more accurately as ‘superimposed acid reflux’. This is an important phenomenon underlying the delay in esophageal clearance, particularly in patients with hiatal hernia.

The literature contains different definitions of the term ‘non-acid’ reflux. However, the definition should be based on the pH of the refluxate, as defined chemically. In cases where the pH falls by at least 1 unit, but does not fall below 4, it is considered the term ‘weakly acidic reflux’. A pH of 7 should be the cut off between ‘weakly acidic’ and ‘non-acid reflux’.

The question arises as to whether a reflux episode should be defined as ‘non-acid reflux’ because it increases the esophageal pH, or ‘weakly acidic reflux’, as the refluxate content is still acidic. A consensus report proposed that the term ‘weakly alkaline reflux’ should be reserved for reflux episodes during which nadir esophageal pH does not drop below 7. Therefore, the previous descriptor ‘non-acid reflux’ can be renamed as ‘weakly alkaline reflux’ that by definition is a very exceptional event. Based on the pH of gastric contents, the majority of reflux episodes constitute weakly acidic reflux.

The prevalence of different types of reflux (acid, weakly acidic and weakly alkaline reflux) in healthy adult subjects has recently been assessed using ambulatory pH-impedance recordings. Normal values of ambulatory 24-hour impedance-pH monitoring were obtained in multicenter studies from adult American and European subjects [38, 39]. These values can now be used in clinical and research settings for comparison with GERD patients.

Good reproducibility of impedance-pH recordings has recently been demonstrated in healthy subjects in standardized, stationary, short-lasting post-prandial studies [40]. The new multicenter European study also demonstrated good reproducibility of 24-hour impedance-pH recordings [39].

The role of acid and weakly acidic reflux in the generation of esophageal typical symptoms (heartburn and regurgitation) has been analyzed in patients with GERD ‘off’ and ‘on’ antisecretory medication with PPIs.

In patients ‘off’ PPI, heartburn, acid taste, and regurgitation were reported during both acid and weakly acidic reflux episodes during a stationary post-prandial pH-impedance study [41]. The presence of any symptom was more common during acid reflux than during weakly acidic reflux. When specific symptoms were analyzed separately, heartburn and acid taste were more commonly linked to acid reflux and regurgitation was reported with similar frequency during acid and weakly acidic episodes. In a 24-hour ambulatory pH-impedance study (in 30 patients with GERD), 200 heartburn episodes were analyzed. In half of them, GER occurred in the preceding 2-min interval (S°R°). The majority (88%) of S°R° involved acid reflux events, whereas weakly acidic accounted for only 12% of all S°R° [42].

When patients with GERD were ‘on’ PPI, a stationary post-prandial pH-impedance study documented a striking decrease in the amount of acid reflux, with continuing post-prandial reflux of weakly acidic gastric contents. Heartburn, the main symptom accompanying acid and weakly acidic reflux in the untreated state, was replaced by regurgitation, which became the predominant symptom during acid-suppressing therapy [41].

Recent ambulatory 24-hour pH-impedance studies assessed persistent symptoms in patients with GERD ‘on’ PPI therapy. These studies showed that acid reflux (incomplete acid secretion blockade by PPI) is associated in 7–28% of persistent symptoms, weakly acidic reflux precedes 30–40% of symptoms which were not preceded by any reflux in 30–60% of cases [43–45]. Patients with symptoms associated with weakly acidic reflux do not have an increased number of these events, suggesting hypersensitivity of the esophagus to such refluxate [45].

The association of weakly acidic reflux with extraesophageal symptoms has been evaluated in infants with...
cardiorespiratory symptoms and more recently in adult patients with chronic cough.

Like in healthy babies, weakly acidic reflux is significantly more frequent than acid reflux in infants with cardiorespiratory symptoms. In 22 infants with recurrent regurgitation or pulmonary problems, pH-impedance studied showed that 90% of reflux events were weakly acidic [46]. However, the causal relationship between weakly acidic reflux and respiratory symptoms remains controversial. In a study in infants with respiratory symptoms, 49 of 165 apnea episodes were accompanied by symptoms, 49 of 165 apnea episodes were accompanied by weakly acidic reflux episodes being 77% of these, weakly acidic [47]. Another study in 19 infants with apnea of prematurity could not confirm the previous finding. A temporal relationship between reflux and a cardiorespiratory event was considered present if both commenced within 20 s of each other. Although apnea and GER were common in these infants, with few exceptions, they did not seem to be temporally related. Only a minority of apneas (3.5%) were associated with reflux reaching the pharyngeal level [48]. So far there is little evidence for an association between apnea and total reflux, acid reflux or non-acid reflux. And no difference has been found between acid GER and non-acid GER in the frequency association with apnea [49].

Acid GER is one of the most important causes of chronic cough. The response to acid suppression in these patients is not as good as in patients with heartburn, but improvement with antireflux surgery has been reported, suggesting the involvement of a non-acidic gastric component in the refluxate. The association weakly acidic reflux cough was studied in 28 patients with chronic cough using 24-hour ambulatory pressure pH-impedance monitoring. Manometry was used for precise recognition of cough. A Symptom Association Probability analysis was performed for each type of reflux (acid and weakly acidic). This study allowed precise determination of the temporal association between cough and GER, and the identification of a subgroup of patients in which chronic cough was clearly associated with weakly acidic reflux [50].

Concurrent impedance and pH recordings can detect significantly more events qualifying as reflux in the pharynx than pH recordings alone. A substantial majority of these events are gaseous refluxes both with and without minor pH drops. A study in a small group of patients showed that gas reflux events with weak acidity appear to be more common among patients with reflux-attributed laryngeal lesions compared to GERD patients and controls [51].

A few studies recently assessed the effect of pharmacologic, endoscopic and surgical antireflux strategies on weakly acidic reflux.

Stationary and ambulatory pH-impedance studies showed that baclofen can reduce both acid and weakly acidic reflux by decreasing the number of TLESRs [52, 53]. It is still not clear whether baclofen can improve persisting symptoms in patients on PPIs due to weakly acidic reflux. Oral alginate preparations are able to decrease the proximal extent of acid and non-acid GER [54].

The endoscopic antireflux procedure EndoCinch has shown to partially reduce acid and weakly acidic reflux and current investigations assess the effect of the Gate-keeper procedure on proximal extent of reflux as measured with pH impedance [55].

To date, there is no published controlled experience using surgical approaches to patients with symptomatic weakly acidic reflux. Theoretically, fundoplication may result in control of symptoms. An initial case report of a patient with chronic cough followed for over 1 year post-fundoplication has documented total resolution of the cough and absence of continuing need for PPI therapy and preliminary experience in patients with a documented symptom relationship to weak acidic reflux episodes (positive symptom index) has revealed a good clinical response to fundoplication [56]. Clinically controlled studies, first performed in specialized centers with experience in pH-impedance monitoring and outcome data, will ultimately define the usefulness of impedance for management of patients with symptom relationship to weakly acidic reflux.

**pH-Bilitec**

Bilitec is a monitoring system that can detect duodenal GER (DGER) by utilizing the optical properties of bilirubin. Although Bilitec does not measure concentrations of duodenal components, a good correlation has been found between bilirubin content and the concentrations of pancreatic enzymes in aspirated refluxate, suggesting that bilirubin is a good tracer for duodenal components in the GER refluxate [57, 58]. The working principle of Bilitec is that detection in the esophageal lumen of any absorption near 450 nm suggests the presence of bilirubin. DGER data measured by Bilitec are usually presented as ‘% time bilirubin absorbance is higher than 0.14’.

Bilirubin monitoring provides a different approach from the other methods of reflux monitoring as it is concerned with the chemical composition of the refluxate. It detects bilirubin in the refluxate, which indicates that DGER has occurred.
Impedance and pH-metry can detect acid and non-acid reflux but cannot describe its composition. In spite of its technical limitations, Bilitec adds information about the chemical nature of acid and non-acid material that refuxes into the esophagus.

Studies using combined pH-Bilitec monitoring have shown that both acid reflux and DGER frequently occur in patients with GERD [59]. A subset of patients with GERD has persistent reflux symptoms and/or esophagitis in spite of standard doses of PPIs. In a group of 33 patients with persistent esophagitis during PPI therapy, 38% had only pathological DGER exposure, and 26% had pathological exposure to both acid and DGER [60].

The antirefl ex effect of pharmacological reduction of TLESRs with baclofen was assessed in 16 patients with persistent reflux symptoms during PPI. These patients had normal acid exposure but persistent pathological DGER. Erosive esophagitis was present in 7 cases and baclofen 20 mg three times daily significantly decreased DGER and the cumulative severity score for reflux symp-
toms [61].

References


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