American Journal of Gastroenterology
ISSN 0002-9270
doi: 10.1111/j.1572-0241.2006.00966.x

Published by Blackwell Publishing

Technology Review: Esophageal Impedance Monitoring

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Intraluminal impedance monitoring is a new technique that can be used to detect the flow of liquids and gas through hollow viscera. In combination with manometry, it is used for esophageal function testing and while manometry provides information on contractile activity, impedance provides information on esophageal bolus transit. This is especially useful in patients with nonobstructive dysphagia. However, impedance monitoring appears to be less suitable for the evaluation of patients with achalasia. When used in combination with esophageal pH monitoring, impedance monitoring makes gastroesophageal reflux monitoring more complete because it allows recognition of both acidic and weakly acidic reflux episodes. The results of several studies suggest that impedance–pH monitoring is useful in the evaluation of patients with PPI-resistant typical reflux symptoms, chronic unexplained cough, excessive belching, and rumination.

(Am J Gastroenterol 2007;102:187–194)

INTRODUCTION

In 1991 impedance monitoring was introduced as a new technique to detect flow of liquids and gas through hollow viscera (1). The landmark publication of Silny triggered various studies in which the possible applications of this technique were investigated. It has now become apparent that impedance monitoring offers new opportunities in the field of esophageal transit testing and gastroesophageal reflux monitoring. In this review we will focus on the clinical applications of this emerging new technique.

REVIEW METHODOLOGY OF PUBLISHED STUDIES

An evidence-based approach was used for this review. A systematic review was performed by us of the medical research published in English from 1966 to July 2006, by using MEDLINE to obtain studies published on esophageal impedance monitoring. The search terms that were included by us were the combination of "impedance" with "esophagus," "reflux," "transit," "swallow," "belch," "aerophagia," "rumination," and "cough." Abstracts corresponding to potentially relevant titles were reviewed, and articles with relevance to principles, practical use, and clinical practice were included. Articles that dealt with applications for pediatric practice were not included. Abstracts presented at national meetings that were not published as full articles were not included.

PRINCIPLES OF IMPEDANCE MONITORING

In electrical impedance monitoring the resistance to electrical flow in an alternating current circuit is measured. In esophageal impedance monitoring, an alternating current circuit is generated between two ring electrodes separated by the nonconductive catheter. Impedance is inversely related to the conductivity of the medium surrounding the two electrodes. The conductivity of air is almost infinitively low and thus a high impedance is measured when the medium consists of air. The conductivity of liquids such as saline or gastric juice is high and impedance is low when these substances form the medium surrounding the electrodes. When the esophagus is empty, the impedance level measured is of intermediate values because of the intermediate conductivity of the esophageal wall. When placing a series of electrodes along a catheter, it is possible to evaluate the direction and velocity in which the medium is transported through the esophagus. Thus, by using esophageal impedance monitoring one can determine the movements of liquids and gas in the esophagus. In esophageal transit tests this is used to measure the clearance of a swallowed bolus; in gastroesophageal reflux monitoring one can measure reflux independent of its acidity. In patients complaining of belching, the nature of their belches can be determined.

ESOPHAGEAL BOLUS TRANSIT

Esophageal manometry is considered the "gold standard" for esophageal motility testing. During esophageal manometry intraluminal pressure sensors (either water perfused or solid state) are used to record pressures generated within the esophageal body and the resting and residual lower esophageal sphincter (LES) pressure during standardized swallows. Manometry offers information on the amplitude and peristaltic progression of esophageal contractions but limited information on the bolus transit (2). Early studies combining manometry and videofluoroscopy have determined that esophageal contractions with an amplitude greater than 30 mmHg are accompanied by complete bolus transit (3). Still, combined manometry and videofluoroscopy studies are difficult to perform in routine clinical practice because of the use of radiation. Combined multichannel intraluminal impedance monitoring and manometry is not subject to this limitation and offers information on esophageal pressure and bolus transit without the use of radiation (Fig. 1) (4).

Studies combining impedance monitoring and videofluoroscopy have validated the accuracy of impedance to determine bolus transit. A study in healthy volunteers by Simren *et al.* found a strong correlation between videofluoroscopy and impedance measurements to estimate the time to esophageal filling ($r^2 = 0.89$; $P < 0.0001$) and time to esophageal emptying ($r^2 = 0.79$; $P < 0.0001$) (5). More recently, Imam *et al.* reported on the correlation between bolus transit parameters as assessed by impedance measurements and fluoroscopy in 13 healthy volunteers indicating that the two techniques yielded concordant results in 97% (72/74) of swallows (6).

Esophageal function testing using combined impedance–manometry in healthy volunteers has been reported by several groups. It is mostly performed with liquid and viscous or semisolid boluses. For liquid, normal saline is often used because the high salt level decreases the impedance level and thus increases contrast with the impedance level of the esophageal wall. It also has identical content worldwide. For viscous boluses a designated gel is commercially available, but the usefulness of such a viscous medium has been disputed. Nguyen *et al.* reported on the dynamics of esophageal bolus transit in 10 healthy subjects who received liquid boluses in the supine and upright positions and semisolid boluses in the supine position (7). Their analysis focused predominantly on bolus head, body, and tail velocities in the pharynx, proximal, middle, and distal third of the esophagus. The authors were able to document that bolus propagation velocities decreased from proximally to distally and that upright position and bolus consistency influenced bolus transit patterns. In a similar study the role of gravity and bolus consistency on esophageal contractions and bolus transit pattern was studied by evaluating these parameters in 10 healthy volunteers positioned at inclinations of 0, 30, 60, and 90 degrees (8). It was found that the distal esophageal contraction amplitude and bolus transit times declined with increasing inclination with an almost perfect negative correlation between the angle of inclination and bolus transit time ($r = 0.99$, $P < 0.02$) for both liquid and viscous. Practically, similar to esophageal manometry, esophageal function testing with combined impedance measurement and manometry is performed in supine position.

Currently normal values for combined impedance–manometry testing have been reported by three groups. Tutuian and coworkers reported normal data from a multicenter study including 43 healthy volunteers (9). Each subject received 10 liquid and 10 viscous swallows at intervals of 20–30 s. Swallows were classified by manometry as (a) *normal peristaltic* (defined as contraction amplitude at both 5 and 10 cm above the LES of at least 30 mmHg and onset velocity in the distal esophagus not greater than 8 cm/s), (b) *simultaneous* (defined as contraction with an onset velocity greater than 8 cm/s or retrograde onset and an amplitude >30 mmHg at both 5 and 10 cm above the LES) and (c) *ineffective* (defined as contraction amplitude in the distal part of the esophagus less than 30 mmHg). Swallows were classified by impedance monitoring as having either (a) *complete bolus transit* (defined as detection of bolus exit in all three distal impedance channels located at 15, 10, and 5 cm above the LES) or (b) *incomplete bolus transit* (defined as bolus retention in at least one of the three distal impedance channels). Using these definitions, more than 93% of normal individuals were found to have at least 80% swallows with complete liquid or at least 70% swallows with complete viscous bolus transit.

In a Dutch–Australian study in 42 healthy volunteers, similar results were found (10). This study used combined water-perfused manometry-impedance catheters and used the characteristics of "supranormal" peristaltic responses (*i.e.,* amplitudes ≥50 mmHg at all sites) to define normal bolus transit. Using these definitions the authors proposed a more liberal definition of normal bolus clearance, namely, complete bolus clearances of at least 70% of liquid swallows and at least 60% of viscous swallows.

The third set of normal data of combined impedance–manometry testing was reported by Nguyen *et al.* in a group of 25 healthy subjects (11). In this study the subjects received saline and semisolid (yogurt) swallows. In addition to bolus transit parameters, which were similar to the previous two studies, the authors also reported on normal value of the esophageal baseline impedance and deglutitive impedance gradient during saline and yogurt swallows.

Using the established normal values (≥80% complete liquid bolus transit and ≥70% complete viscous bolus transit) the yield of esophageal function testing was investigated in a group of 350 patients presenting with various esophageal symptoms and having various manometric findings (12). In this group of patients, abnormal bolus transit was found in all patients with achalasia and scleroderma, proving the principle that impedance can assess bolus transit in patients with severe esophageal motility abnormalities. On the other hand, almost all (*i.e.,* ≥95%) patients with normal esophageal manometry, nutcracker esophagus, and isolated LES abnormalities (*i.e.,* hypertensive, hypotensive, and poorly relaxing LES) had normal bolus transit for liquid. In the groups of patients with ineffective esophageal motility (IEM) and diffuse esophageal spasm (DES), approximately half of the patients had normal bolus transit.

Conchillo *et al.* reported on the results of combined impedance–manometry testing in 40 patients with nonobstructive dysphagia (13). Based on the manometric data these patients were classified as having normal motility (20), IEM

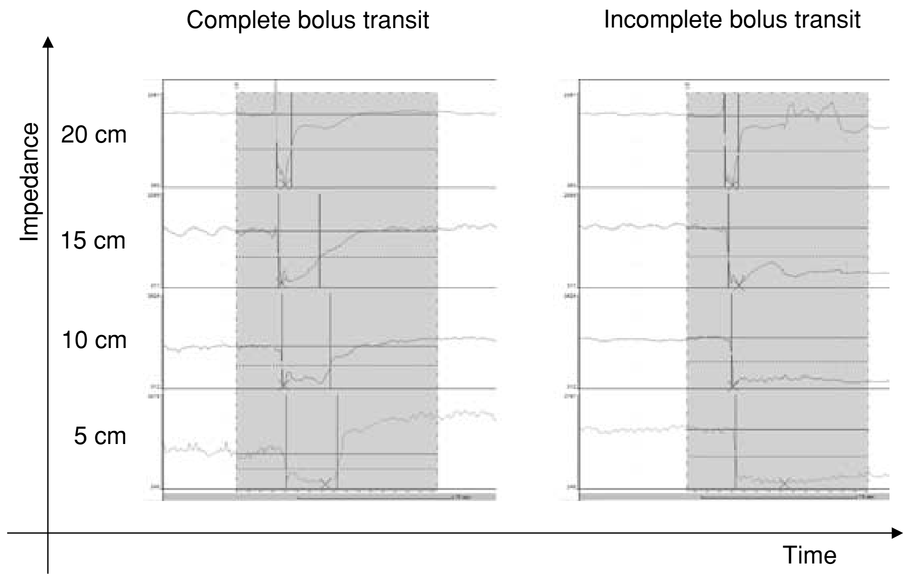

Figure 1. Example of impedance tracing of complete and incomplete bolus transit.

(13), DES (4), and achalasia (3). Bolus transit was judged to be normal if ≥80% liquid swallows and ≥70% viscous swallows showed complete bolus transit. In this group of patients, abnormal transit for liquid and/or viscous boluses was found in 35.3% of patients with normal motility, in 66.7% of DES patients, and in 100% of achalasia patients. These findings allowed the authors to conclude that the addition of impedance to manometry identifies esophageal function abnormalities in patients with nonobstructive dysphagia in which manometry would have been normal or unspecific. However, the question arises whether a similar conclusion can be drawn when impedance monitoring is compared with high-resolution manometry, as it has been shown that the latter technique also identifies motility abnormalities not detected by conventional manometry (14).

A more detailed study in 70 patients with IEM identified that there is no perfect (*i.e.,* highly sensitive and highly specific) manometric cutoff that would predict complete bolus transit and that the current manometric criteria for diagnosing IEM (*i.e.,* ≥30% manometric ineffective swallows) is too sensitive and lacks the specificity of identifying patients with abnormal bolus transit (15). Normal bolus transit in the group of patients with IEM appeared to be dependent on the distal esophageal contraction amplitude (*i.e.,* average amplitude at the esophageal sites 5 and 10 cm above the LES), the number of sites with low contraction amplitudes, and the overall number of manometric ineffective swallows. Another important finding of this study was that approximately one-third of patients with IEM had normal bolus transit for liquid and viscous (suggesting a mild functional defect), approximately one-third had abnormal bolus transit for either liquid or viscous (*i.e.,* moderate functional defect), and the remaining third of IEM patients had abnormal bolus transit for both liquid and viscous (*i.e.,* severe functional defect).

A similar detailed analysis in 71 patients with DES indicated that approximately half of the patients fulfilling the manometric criteria for DES have normal bolus transit for both liquid and viscous swallows (*i.e.,* no functional defect). About 25% of DES patients had abnormal bolus transit for both liquid and viscous (*i.e.,* severe functional defect) and the other 25% had abnormal bolus transit for either liquid or viscous (*i.e.,* moderate functional defect) (16). The investigators also noticed manometric and bolus transit differences between DES patients presenting with chest pain and patients presenting primarily with dysphagia. Patients presenting primarily with chest pain had higher contraction amplitudes and a higher proportion of swallows with normal bolus transit time when compared with patients presenting primarily with dysphagia. Based on these observations one can speculate that DES patients with chest pain, higher amplitude contractions, and normal transit should be managed differently than DES patients with dysphagia, lower amplitude contractions, and abnormal transit.

It is not felt likely that esophageal impedance monitoring will replace barium swallows. Although fluoroscopy has the disadvantage of exposing the patient to ionizing radiation, it provides both functional and anatomical information, while with impedance monitoring only functional information is attained. Furthermore, swallows of solid material can be studied fluoroscopically, which is not possible with impedance monitoring. Thus far, no studies have directly compared the two techniques in patients with esophageal symptoms.

Impedance monitoring does not seem to be very useful for the diagnosis of achalasia and for the follow-up evaluation of esophageal emptying in achalasia patients. Because 100% of the manometrically diagnosed achalasia patients have an abnormal emptying pattern during esophageal function testing and no achalasia-specific impedance abnormalties have yet been reported, impedance monitoring does not contribute to the diagnosis of achalasia (12, 13, 17). A comparative study using fluoroscopy and impedance monitoring for assessment of the height of the fluid column and bolus clearance time after a barium swallow revealed a poor-to-moderate correlation between the two techniques (18). The authors concluded that low baseline impedance levels and air entrapment in the esophagus limit the value of impedance monitoring for assessment of esophageal emptying in achalasia patients.

In summary, current data support the concept that combined impedance monitoring and manometry can be used in research and clinical settings to provide more detailed information on esophageal function. The next step in evaluating the clinical utility of the additional information provided by impedance monitoring is using this technique in interventional outcome studies. These studies would allow a critical evaluation of the proposed parameters and allow quantification of the predictive value of the information provided by impedance measurements.

GASTROESOPHAGEAL REFLUX

Besides detection and quantification of bolus transport in an aboral direction such as is performed during esophageal function testing, impedance monitoring is also useful to detect the occurrence of gastroesophageal reflux. Esophageal impedance monitoring identifies oral bolus movement and makes it possible to detect the nature (liquid, gas, or mixed liquid–gas) and proximal extent of gastroesophageal reflux (Fig. 2). It is important to stress that measurements of the refluxate with impedance monitoring are independent of acidity. Combined with pH-metry, one can determine whether a reflux episode is acid (nadir pH <4), or nonacid (nadir pH >4). Nonacid reflux can further be separated into weakly acidic (nadir pH 4–7) or weakly alkaline (nadir pH >7) (19). Usually pH and impedance monitoring are performed conjointly and it has been shown that assessment of reflux with impedance measurement is as reproducible as pH-metry (20). Indications for reflux monitoring using impedance–pH monitoring are listed in Table 1 and will be discussed below.

Normal values for 24-h impedance–pH monitoring have been reported from three independent multicenter studies (21–23) (Table 2). It is uncertain, however, whether weakly acidic reflux episodes can cause damage to the esophagus or that the total number of weakly acidic reflux episodes predicts whether the patient's symptoms are caused by these. Therefore it is questionable whether quantifying weakly acidic reflux episodes in patients with gastroesophageal reflux disease (GERD) and comparing this with normal values is useful. More is to be expected from investigating the temporal relation between the onset of symptoms and the occurrence of reflux episodes.

Vela *et al.* performed pH–impedance studies in 12 GERD patients off therapy and repeated these studies while these patients were on omeprazole 20 mg b.i.d. (24). Symptoms were found to be produced by both acid reflux and nonacid reflux. Although heartburn and acid taste were more likely related to acid reflux, the occurrence of regurgitation was not reduced at all during acid-suppressive therapy. This study suggested that

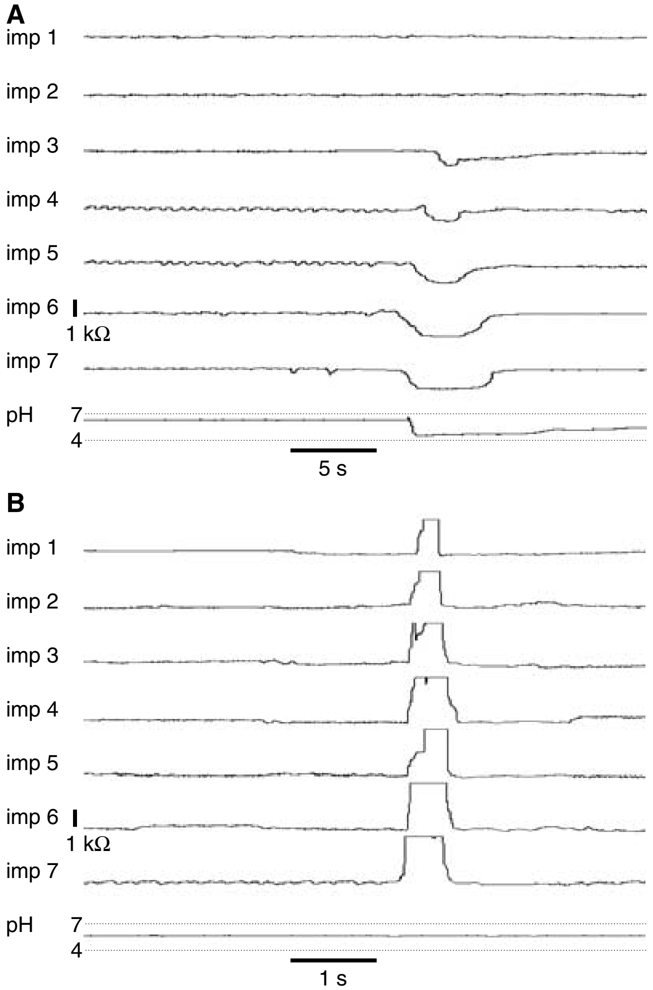

Figure 2. Esophageal impedance and pH signals. A retrograde moving decrease in impedance is observed from the most distal segment (imp 7) reaching segment 3, indicating liquid reflux. The pH does not drop below 4, and this episode is therefore characterized as weakly acidic. Panel B shows a retrograde moving increase in impedance, indicating pure gas reflux. Note that the time scales are different in panel A and B.

impedance–pH monitoring may be useful in the evaluation of patients with persistent symptoms under proton pump inhibitor (PPI) therapy. A large multicenter study in which 24-h pH–impedance monitoring was carried out in 168 patients with PPI-resistant symptoms showed that 16 (11%) of the 144 patients who had symptoms during the measurement had a positive symptom index (SI) for acid reflux and 53 (37%) had a positive SI for nonacid reflux. Thus, reflux could be identified as the cause of symptoms in 69 patients (48%) based on the combined pH–impedance data and in 16 patients based on pH-metry alone (25). These data suggest that combined pH–impedance monitoring makes it possible to identify more patients in whom reflux is the cause of their symptoms under PPI therapy compared with pH-metry alone. Similar results were obtained by Zerbib and colleagues (26). The results of a recent study suggest that a positive SI for weakly acidic

Table 1. Indications for Gastroesophageal Reflux Monitoring Using Impedance

Indications for Assessment of Gastroesophageal Reflux Using Impedance Monitoring
Reflux symptoms resistant to inhibition of acid secretion
Unexplained chronic cough
Suspicion of rumination
Excessive belching
Reflux symptoms in achlorhydria

reflux predicts the response to antireflux surgery (27). Of the 18 patients that were followed after a laparoscopic fundoplication, 16/17 (94%) with a positive SI during preoperative pH–impedance monitoring under PPI therapy reported that their symptoms were improved 14 months postoperative while the one patient with a negative SI experienced persistent reflux symptoms. More studies are required to confirm the findings of this uncontrolled outcome trial.

Before the introduction of impedance monitoring, patients with persistent symptoms under PPI therapy were often measured with pH-metry alone after patients discontinued their antisecretory therapy for at least 7 days. This allowed physicians to evaluate whether the patient's symptoms were truly as a result of gastroesophageal reflux, as indicated by a positive SI for acid reflux. Preoperative examinations before antireflux surgery are also carried out after patients stopped their PPI therapy, as esophageal acid exposure is a strong predictor of the success of antireflux therapy. Ambulatory monitoring on PPI therapy allows investigating whether acid secretion is indeed adequately suppressed. Comparative studies between the yield of impedance–pH monitoring without discontinuation of antisecretory medication and pH-metry after discontinuation of therapy have not been performed yet. It is thus still unclear which approach is optimal for the workup of a patient with PPI-resistant reflux symptoms. Ambulatory 24-h impedance–pH studies in GERD patients who stopped their therapy revealed that the vast majority of the symptomatic reflux episodes in these patients were acidic and it has been shown that only approximately 15% of the heartburn and regurgitation episodes in patients off therapy were as a result of weakly acidic reflux (28, 29). It appears that the merits of the addition of impedance measurement to pH-metry to investigate typical reflux symptoms off therapy are small but some patients do have a positive relationship between

Table 2. Published Normal Values of Ambulatory 24-h pH-Impedance Monitoring

	N	Acid (pH <4)	Weakly Acidic (pH 4–7)	Weakly Alkaline (pH <7)	Total
Shay (21)	60	18 (59)	9 (26)	0 (1)	30 (73)
Zerbib (22)	68	22 (50)	11 (33)	3 (15)	44 (75)
Zentilin (23)	25	18 (51)	14 (38)	4 (18)	16 (48)

In the study of Shay *et al.* acid reflux episodes are divided into acid reflux episodes and superimposed acid reflux episodes.

Numbers are presented as median (95th percentile).

symptoms and weakly acidic reflux after discontinuation of PPIs (26, 30). Also, symptom association analysis performed separately for acidic and weakly acidic reflux does not result in a higher yield than symptom association analysis for all reflux episodes pooled, independent of pH. Furthermore, it has been reported that impedance monitoring identified weakly acidic reflux as a cause of reflux symptoms in a patient with achlorhydria as a result of autoimmune atrophic gastritis (31).

Studies using ambulatory pH-metry showed that (acid) reflux can be the cause of chronic cough (32, 33). In 22 patients with chronic cough, Sifrim *et al.* investigated the role of weakly acidic reflux using combined pH–impedance monitoring (34). Of these 22 patients, five patients suffered from acid reflux-induced cough, three from weakly acidic-induced cough and two had cough episodes after both acid and weakly acidic reflux episodes. Thus, in the three patients with cough episodes induced by weakly acidic reflux, the cause of their cough could only be identified by impedance monitoring. This suggests that impedance monitoring is useful in addition to pH-metry for the evaluation of patients with chronic cough. Recently, it has been reported that patients with weakly acidic reflux-induced coughing responded favorably to antireflux surgery (35).

Recently, a system was developed that allows one to monitor esophageal pH during prolonged periods of time without the need for transnasal intubation (Bravo®, Medtronic, Minneapolis, MN). Radiofrequency signals are transferred from a capsule attached to the mucosa of the distal esophagus to an external portable recording device. As this technique is much better tolerated by patients than conventional catheter-based pH monitoring, recording time can usually be extended to 48 h (36). This leads to an increase in the sensitivity for the detection of GERD (37). However, as with this technique only esophageal pH is measured, it suffers from the same limitations as catheter-based pH monitoring; only reflux with a pH less than 4 is detected.

RUMINATION

Combined pH–impedance monitoring has been used in esophageal disorders other than GERD. According to the Rome II criteria, rumination is defined as a chronic or recurrent regurgitation of recently ingested food into the mouth with subsequent remastication and swallowing present for at least 3 months in the absence of nausea and vomiting (38). Rumination is usually discontinued when the contents become acidic. It is believed to be an involuntary learned behavior, and no alterations in gastric function could be observed (39). Rumination is often mistaken for GERD, but in contrast to GERD PPI therapy can increase symptoms. Documentation of rumination is difficult with pH-metry and it has therefore been suggested that rumination is a clinical diagnosis. Because of the nonacidic nature of the regurgitated content, impedance monitoring seems a promising tool to investigate patients with presumed rumination. It has recently been

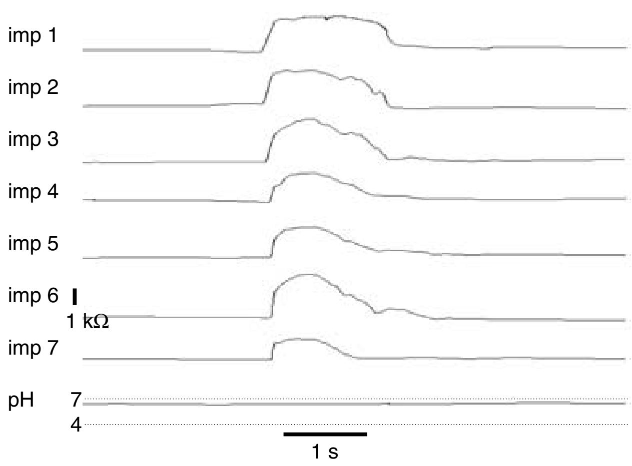

Figure 3. This example shows a supragastric belch. Air is rapidly entering the esophagus from proximally and is expelled almost immediately thereafter in the oral direction.

shown that the combination of esophageal impedance measurement and manometry with intragastric pressure transducers makes it possible to document the sequence of events leading to regurgitation (40). An increase in gastric pressure initiates the reflux events, which can be identified on impedance. Impedance makes it thus possible to objectively identify patients with rumination.

BELCHING

Impedance has also been measured in patients with excessive belching. Belching is a common symptom, often associated with conditions such as GERD and dyspepsia (41). In some patients, belching occurs as an isolated symptom and is called aerophagia. While some of these patients are convinced that their belching results from a gas-producing intragastric process such as fermentation, most physicians attribute the excessive belching to anxiety and excessive air-swallowing (42). With esophageal impedance monitoring it has been shown that these patients actually do not swallow air but suck air into the esophagus after which they expel this air almost immediately (43). The belches of these patients do not originate from the stomach and the ingested air does not reach the stomach; they can be designated as supragastric belches (Fig. 3). Impedance monitoring makes it thus possible to distinguish the patients with supragastric belching from those with a high number of normal gastric belches. This can be useful because the patients with supragastric belching are likely to benefit from behavioral therapy.

CONCLUSIONS

Combined measurement of impedance and pressure in the esophagus appears to be a useful technique to evaluate esophageal bolus transit. From the patient's perspective, combined impedance/pressure recording is not more invasive than conventional manometry. The investigator or clinician obtains information on both esophageal peristalsis and bolus transit during the same swallow. Unlike videofluoroscopy, impedance measurement does not provide data on structural abnormalities in or around the esophagus but the technique allows quantification of bolus transit data without the use of radiation. Impedance monitoring for esophageal function testing has been validated, normal values for combined impedance–manometry are available from different centers, and this technique yielded more information than manometry alone in patients with esophageal motility abnormalities. However, outcome data are required before conclusions on the clinical utility of the additional information provided by impedance–manometry testing can be drawn. It is, for example, not known whether patients with normal findings on manometry but impaired esophageal emptying on impedance monitoring are more at risk for experiencing dysphagia after antireflux surgery.

The combination of pH and impedance monitoring can be used to detect acidic and weakly acidic reflux. For the patient 24-h impedance and pH recording carried with a single catheter does not result in higher discomfort than pH monitoring alone. Normal values were published. The list of potential indications for impedance–pH monitoring is expanding and now incorporates PPI-resistant typical reflux symptoms, chronic unexplained cough, excessive belching, and suspicion of rumination.

In conclusion, intraluminal impedance monitoring has been shown to be a useful tool to measure esophageal transit and gastroesophageal reflux in health and disease. The authors believe that this technique already deserves a place in the diagnostic armentarium of the twenty-first century gastroenterologist. However, the principles of evidence-based medicine dictate that the results of properly designed outcome studies have to be awaited before firm recommendations can be made.

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Received May 29, 2006; accepted September 12, 2006.

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CONFLICT OF INTEREST

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