

# Use of Esophageal Impedance beyond Diagnosis of GERD

## Abstract

Combined multichannel intraesophageal impedance-pH (MII-pH) monitoring is currently the gold standard method to diagnosis of gastroesophageal reflux disease (GERD). A standard MII-pH catheter has six pairs of impedance electrodes. Multiple impedance-measuring within the esophagus allows determination of direction of bolus movement within the esophagus. So that MII is used as a good esophageal functional test in the diagnosis of swallow, belching, aerophagia and regurgitation.

Baseline impedance value has been considered is a marker of transepithelial resistance measured in vitro, which is indicating esophageal epithelial integrity. It has been shown that distal baseline impedance values are correlated with esophageal acid exposure in GERD patients. In addition, baseline impedance values has been studied in the patients with disorders rather than GERD such as eosinophilic esophagitis, esophageal motor disorders and effect of radiofrequency ablation treatment in Barrett's esophagus. In this article, MII-pH is reviewed its clinical applications beyond the diagnosis of GERD.

## Review Article

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## Introduction

Since its advent in the early 1990s, MII-pH monitoring has been the gold standard for diagnosis of GERD [1]. This widely adopted technique has superseded the use of isolated intraesophageal pH monitoring by its ability to detect and localise intraesophageal boluses, and further classify reflux activity beyond conventional acid reflux, by differentiating reflux events into gas versus liquid episodes.

The modus operandi of MII monitoring is the measurement of electrical conductivity. An alternating electric current is passed between pairs of electrodes mounted onto a specialised nasogastric catheter. The adjacent intraluminal material conducts the current. In the empty, collapsed esophagus, the esophageal mucosa is the agent providing electrical resistance as it lies in direct contact with the catheter. Ionic liquid conducts electricity well, thus its intraesophageal presence generates lower impedance readings to reflect reduced electrical resistance. In contrast, gaseous material is an electrical insulator which translates into high intraluminal impedance when it passes by said electrodes. Liquid boluses can be further characterised into acid versus non-acid episodes by the combination of MII with pH sensing.

Furthermore, impedance measurement can ascertain the direction of bolus travel within the esophagus. This is due to the presence of multiple pairs of electrodes conducting the aforementioned current placed at standardised intervals. A standard MII-pH catheter has six pairs of impedance electrodes. Antegrade bolus movement, i.e. what happens on swallowing, is detected by changes in impedance progressing chronologically from the proximal sensors to their distal counterparts. Conversely, retrograde bolus transit (i.e. reflux) manifests as changes in impedance progressing proximally.

The versatile diagnostic capabilities of impedance measurement render it a potentially valuable tool in evaluating

many other common esophageal disorders. In this article i review its clinical applications beyond the diagnosis of GERD.

## Belching: Gastric Versus Supragastric

Not all retrograde flow patterns of gaseous boluses are equal. The advanced study of impedance monitoring has revealed that there are two types of belching: the gastric belch and the supragastric belch.

The gastric belch is a vagally generated reflex leading to relaxation of the lower esophageal sphincter. Intra gastric air is expelled through the esophagus and out through the mouth. It is accepted that gastric belches are physiological events. A gastric belch shows up on impedance monitoring as a one-way incline progressing distal to proximal, from left to right. During the supragastric belch, pharyngeal air is subconsciously sucked or injected into the esophagus, then expelled again without reaching the stomach. This is not to be confused with aerophagia, where the subject swallows air into the stomach. Supragastric belches can be observed on impedance tracings whereby there is antegrade movement of air down into the distal esophagus, followed seconds later by venting of this same gaseous bolus back up through the esophagus and out through the mouth. This results in the characteristic 'V' shaped pattern of flow on impedance monitoring.

In 2004, Bredenoord et al were the first to demonstrate the difference between the two belching subtypes [2]. Prior to this, conventional wisdom dictated that excessive belching was purely the venting of air from the stomach after a period of excessive air swallowing. This study examined 14 healthy volunteers and 14 patients with complaints of excessive belching. The rate of swallowing and the incidence of air swallowing were similar in patients and controls. While gastric belches were found both in patients and healthy volunteers, supragastric belch was only observed in patients and not in controls. None of these

supragastric belches was accompanied by gastroesophageal reflux.

### Accurate diagnosis guides treatment

The distinction between gastric and supragastric belching is important because it is now understood that the therapeutic approach to the two disorders are different. This can be intuited from their disparate aetiologies. Excessive and problematic gastric belching is relieved by agents that inhibit transient LES relaxation, the commonest being baclofen. Supragastric belching will not respond the same way as it is not a consequence of LES dysfunction. Instead, supragastric belching arises from pathological air sucking, thus its correction requires behavioural modification. This can be achieved by biofeedback therapy. The patient can be trained to be aware, by watching their impedance monitoring in real-time, of their habit of sucking air into their esophagus, and is able to take steps to consciously repress this tendency.

The combination of MII with high resolution manometry (HRiM) allows synchronous measurement of bolus transport and esophageal clearance without the use of radiation. HRiM is also useful in evaluating aerophagia. Aerophagia is classified as a swallow together with a rapid impedance increase of 1000 ohm with this technique. Combined with manometry, impedance technique allows a better time definition between increased abdominal pressure and regurgitation events. The differential diagnosis could be easily between reflux, rumination, belching and aerophagia. Blondeau et al. performed a study were taken from 12 patients with clinically suspected rumination or supragastric belching using HriM [3]. They examined baclofen (10 mg, 3 times daily) effect on reflux, rumination, supragastric belching and aerophagia. In this study, the number of flow events 473 at baseline (42 reflux, 192 rumination, 188 supragastric belching, and 42 aerophagia) was significantly reduced to 282 (32 reflux, 99 rumination, 123 supragastric belching, and 13 aerophagia) during baclofen therapy ( $P=0.02$ ). They suggested that baclofen is an effective treatment for patients with rumination or supragastric belching/aerophagia.

### Aetiology of supragastric belching

**Meals:** The average rate of supragastric belching in Bredenoord's study was shown to be lower preprandially than postprandially, but this was not a statistically significant difference (40.9 vs 67.7). The investigators concluded that meals do not influence supragastric belches.

**Psychological factors:** Attention, or the lack thereof (i.e. distraction), also appears to impact upon the frequency of belches in symptomatic patients, which highlights the relevance of psychological factors in supragastric belching [4]. A Greek study showed that gastric belching is not affected by diurnal variation, but supragastric belches almost cease at night, suggesting the presence of a behavioral disorder [5].

**Motility:** Silva et al. [6] studied esophageal motility in 16 patients with troublesome belching and 15 controls [6], on the hypothesis that symptomatic patients demonstrate aberrant patterns of esophageal contractions and bolus transit. The study disproved the former premise (there was no difference in esophageal contractions between patients and controls) but did identify

abnormal bolus transit in patients compared to controls, whereby the ingested bolus travelled slower through the proximal and middle esophageal body, then crossed the distal esophageal body faster [5].

### Belching and GERD

Patients with GERD often have increased frequency of belching. It has been reported that air swallowing promotes belching but does not facilitate acid reflux in healthy volunteers [7]. Bredenoord et al. [8] studied 12 controls and 12 patients with GERD, before and after intragastric inflation of 600 mL of air. There was a higher frequency of air swallowing in the patient group compared to healthy controls, and the consequent larger intragastric air bubble also led to more frequent belching [8]. The proposed mechanism is that patients with GERD swallow more often than healthy subjects by responses to perceived reflux events [9]. However no relationship between the occurrence of acid reflux and number of belches. We understand that gastric belching and acid reflux are not causally related.

Hemmink et al. investigated the relationship between the number and type of reflux episodes and supragastric belches during ambulatory 24-h MII-pH monitoring off proton pump inhibitor therapy in 50 patients with typical reflux symptoms and 10 healthy volunteers. They found that patients with reflux symptoms were more prone to supragastric belching, and that 48% of supragastric belches occurred in close temporal association with reflux episodes [10]. The authors suggested that supragastric belching accomplishes reflux as a result of abdominal straining or by provoking TLESRs.

### Esophageal Motor Disorders and Impedance

#### Low baseline impedance in identification of esophageal disorders

The impedance between two electrodes depends not only upon luminal contact but also mucosal integrity, wall thickness and cross sectional area. The baseline impedance value is considered a reasonable surrogate of transepithelial resistance measured in vitro, which itself represents underlying esophageal epithelial integrity [11]. Distal baseline impedance values have been found to correlate inversely with esophageal acid exposure in GERD patients - more acid exposure leads to lower baseline impedance. The relationship appears to be causal, and evidence for this lies in the ability of PPI therapy to significantly increase baseline impedance [12].

Impedance levels in patients with ineffective esophageal motility are also lower than in healthy controls [13], as studied in patients with eosinophilic esophagitis, various esophageal motor disorders, and previous radiofrequency ablation treatment in Barrett's esophagus [12,14-16]. As alluded to earlier, baseline impedance values as a marker of esophageal epithelial integrity is dependent on the characteristics of the collapsed esophageal wall. Blonski et al. analyzed MII and manometry studies in patients with abnormal manometry, nutcracker esophagus ( $n=20$ ), distal esophageal spasm, ( $n=20$ ), ineffective esophageal motility (IEM,  $n=20$ ), achalasia ( $n=20$ ), and systemic sclerosis affecting the esophagus ( $n=10$ )<sup>13</sup>. They calculated average values of esophageal

impedance measured at 5 and 10-cm above the lower esophageal sphincter before liquid swallows [distal baseline impedance (DBI)], after 10 liquid swallows [distal liquid impedance (DLI)], and after 10 viscous swallows [distal viscous impedance (DVI)].

DBI, DLI, and DVI were significantly lower in patients with achalasia and systemic sclerosis than healthy volunteers with normal esophageal manometry. The authors also found that patients with IEM had significantly lower DBI, DLI, and DVI than healthy volunteers or patients with nutcracker esophagus and significantly higher DVI than patients with achalasia. Lower baseline impedance levels were described in patients with IEM than in healthy controls [13].

Interestingly, the mean DBI, DLI, and DVI in patients with IEM were not significantly different from those found in patients with systemic sclerosis. These results might suggest some level of fluid retention within the esophagus in patients with IEM, similar to that found in achalasia. Furthermore, the low distal esophageal impedance values in patients with IEM and achalasia are speculated to reflect the inflammation caused by fluid retention within esophageal mucosa.

The mean DBI, DLI, and DVI values in patients with DES were not significantly different than those observed in healthy volunteers. This might be explained by the heterogeneity within the DES group with regard to esophageal pressure and bolus transit.

In their discussion, the authors suggested that esophageal impedance might be a useful parameter to evaluate fluid retention and may assist in the diagnosis of esophageal motility abnormalities. This recommendation has been echoed by other groups that showed decreased distal esophageal baseline impedance levels in achalasia that may help identify chronic fluid retention [17-19]. In other words, low baseline impedance values help identify a diseased esophagus, whether that is due to altered esophageal motility, mucosal inflammation, or chronic fluid retention as in achalasia.

### Impedance in dynamic assessment of esophageal clearance

Nguyen et al. [18] also explored the potential clinical utility of impedance monitoring in assessing esophageal emptying in achalasia [18]. Their study found failed bolus transport through the esophagus, luminal content regurgitation in 35% of the swallows, and impedance evidence of pathological air movement within the proximal esophagus during deglutition in 38% of the swallows. In addition, a good correlation has been established between esophageal impedance measurements and videofluoroscopic assessment in evaluating esophageal clearance [20].

Mainie et al. performed combined MII-manometry on patients with systemic sclerosis (n=15) and achalasia (n=20), and recruited subjects with poorly relaxing lower esophageal sphincter (LES) with normal esophageal body function (n=20) as a control group [21]. They found that overall bolus transit is impaired in both patients with achalasia and systemic sclerosis, as a result of abnormal esophageal body contraction and not abnormal LES relaxation. Segmental bolus stasis in patients with achalasia and scleroderma caused bolus transit abnormalities in this study.

### Eosinophilic esophagitis and impedance

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus that leads to fibrosis and structural changes within the esophagus. Patients with EoE most frequently report symptoms of dysphagia, food impaction, chest pain and sometimes heartburn. It has been postulated that esophageal mucosal integrity is impaired in patients with EoE [22,23]. van Rhijn et al. [14] studied esophageal baseline impedance levels in EoE patients and in controls. The relationship between baseline impedance levels and esophageal acid exposure was also examined as a potential causal mechanism [14]. Eleven adult patients with histologically confirmed EoE and a history of dysphagia and/or food impaction were included, and 11 controls matched to the EoE patients by total acid exposure time. Baseline impedance levels were assessed every 2 hours during a 30-second time period. The median baseline impedance level during all 2-hour periods was considered to be the baseline impedance level for the measurement.

Baseline impedance levels in EoE patients were markedly lower compared to controls in the distal esophagus, mid-esophagus and proximal esophagus (p=0.005). While baseline impedance decreased from proximal to distal in healthy subjects, there was no such gradient in patients with EoE. Because baseline impedance values are decreased throughout the esophagus in patients with EoE without favouring the distal esophagus, the authors concluded that impaired mucosal integrity in EoE is likely to be a function of factors beyond pure acid reflux. However baseline impedance monitoring remains clinically advantageous as a marker both of disease activity and therapeutic monitoring.

### Rumination

The rumination syndrome is a functional gastroduodenal disorder that is characterized by near-immediate regurgitation of ingested food and the rechewing and reswallowing of said food. Rumination events are induced by a rise in intra-gastric pressure generated by a voluntary but unintentional contraction of the abdominal wall musculature.

The utility of HRiM in delineating esophageal motility and bolus transit has extended to elucidating the rumination syndrome. Rommel et al. [24] subjected 16 patients with clinically suspected rumination to HRiM for one hour after a solid-liquid meal [24]. Only 50% (8/16) were proven on HRiM to have actual rumination; the others were found to have postprandial belching and regurgitation.

A novel diagnostic classification for the rumination syndrome has been proposed which utilises HriM [25], based on the investigation of 12 patients with rumination syndrome and 12 patients with GERD who presented with predominant symptoms of regurgitation. In this study, abdominal pressure peaks exceeding 30mmHg during proximal reflux episodes were not observed in any patients with GERD, but seen in all of the rumination group. Furthermore, amplitudes over 30mmHg were observed in 70% of individual gastric pressure peaks during proximal reflux events in the rumination cohort.

This paper describes three different mechanisms of rumination. The first mechanism, 'primary rumination', is denoted

by a rise in intraabdominal pressure that preceded retrograde flow. This occurs in 100% of patients with rumination. 'Secondary rumination', affecting 45% of patients, is similar to a primary rumination event, but the increase in abdominal pressure occurs after the onset of a reflux event. The third mechanism is termed supragastric belch-associated rumination, seen in 36% of patients.

Barba et al. recently reported that rumination can be effectively corrected by biofeedback-guided control of abdomino-thoracic muscular activity [26]. They prospectively studied 28 patients fulfilling the Rome criteria for rumination syndrome who then had their diagnoses confirmed on intestinal manometry (showing abdominal compression associated with regurgitation). These patients underwent three electromyography (EMG)-guided biofeedback training sessions within a 10-day period, complemented by instructions for daily home exercises, with good results.

### Barrett's Esophagus and Impedance

In patients with Barrett's esophagus, it is recognized that analysis of esophageal impedance tracings is hampered by low esophageal baseline levels, impeding reliable assessment of reflux episodes [27]. Very low impedance baseline which are very likely to occur abnormal esophageal mucosa in patients with Barrett's esophagus. Baseline impedance has been recently considered to be related to esophageal integrity. Another explanation is the occurrence of large numbers of reflux episodes in patients with Barrett's can result in an increased conductivity and therefore decreased impedance. Hemmink et al. [16] examined the effect of radiofrequency ablation (RFA) on esophageal baseline impedance in 15 patients with Barrett's esophagus [16]. They found that RFA increased baseline impedance in all recording segments in the upright position, in the supine position, although it didn't to reach statistically significant levels. They have shown that baseline impedance levels increased after conversion into neosquamous epithelium.

### Functional Heartburn and Impedance

Functional heartburn (FH) is an exclusive diagnosis and is defined by the Rome III criteria as a burning retrosternal discomfort, excluding GERD and esophageal motility disorders as a cause of the symptom. The advent of MII-pH monitoring has allowed us to subdivide the heterogeneous subgroups of patients within the group of nonerosive reflux disease. The absence of visible lesions on endoscopy, normal distal esophageal acid exposure and absence of troublesome reflux-associated (to acid, weakly acidic or non-acid reflux) is subclassified FH. Martinucci et al studied baseline impedance levels in patients with FH divided into two groups on the basis of symptom relief after PPIs [28]. In this study 30 patients with a symptom relief higher than 50% after PPIs composed Group A, and 30 patients, matched for sex and age, without symptom relief composed Group B, a group of 20 healthy volunteers (HVs) was enrolled. Group A (vs Group B) showed an increase in the mean AET mean reflux number, proximal reflux number, acid reflux number. Baseline impedance levels were lower in Group A than in Group B and in HVs ( $p < 0.001$ ). The authors concluded that evaluating baseline impedance levels could improve the distinction between FH and hypersensitive

esophagus. Kohata et al. also showed that among patients with PPI-refractory nonerosive reflux disease, acid-reflux type is associated with lower baseline impedance compared with non-acid-reflux type and functional heartburn [29]. They suggested baseline impedance value may be useful for the classification of PPI-refractory patients.

### References

1. Sifrim D, Castell D, Dent J, Kahrlas PJ (2004) Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut* 53(7): 1024-1031.
2. Bredenoord AJ, Weusten BLAM, Sifrim D, Timmer R, Smout AJPM (2004) Aerophagia, gastric and supragastric belching: a study using intraluminal electrical impedance monitoring. *Gut* 53(11): 1561-1565.
3. Blondeau K, Boecxstaens V, Rommel N, Farre R, Depeyter S, et al. (2012) Baclofen Improves Symptoms and Reduces Postprandial Flow Events in Patients With Rumination and Supragastric Belching. *Clin Gastroenterol Hepatol* 10(4): 379-384.
4. Bredenoord AJ, Weusten BLAM, Timmer R, Smout AJ (2006) Psychological factors affect the frequency of belching in patients with aerophagia. *Am J Gastroenterol* 101(12): 2777-2781.
5. Karamanolis G, Triantafyllou K, Tsiomoulos Z, Polymeros D, Kalli T, et al. (2010) Effect of sleep on excessive belching A 24-Hour Impedance-pH Study. *J Clin Gastroenterol* 44(5): 332-324.
6. Silva AC, Aprile LR, Dantas RO (2013) Esophageal motility in troublesome belching. *Arq Gastroenterol* 50(2): 107-110.
7. Bredenoord AJ, Weusten BL, Timmer R, Akkermans LM, Smout AJ (2005) Relationships between air swallowing, intragastric air, belching and gastro-oesophageal reflux. *Neurogastroenterol Motil* 17(3): 341-347.
8. Bredenoord AJ, Weusten BL, Timmer R, Smout AJ (2006) Air swallowing, belching, and reflux in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 101(8): 1721-1726.
9. Hemmink GJ, Weusten BL, Bredenoord AJ, Timmer R, Smout AJ (2009) Increased swallowing frequency in GORD is likely to be caused by perception of reflux episodes. *Neurogastroenterol Motil* 21(2): 143-148.
10. Hemmink GJM, Bredenoord AJ, Weusten BLAM, Smout AJPM (2009) Supragastric belching in patients with reflux symptoms. *Am J Gastroenterol* 104(8): 1992-1997.
11. Farre R (2013) Pathophysiology of gastro-esophageal reflux disease: a role for mucosa integrity? *Neurogastroenterol Motil* 25(10): 783-799.
12. Kessing BF, Bredenoord AJ, Weijenborg PW, Hemmink GJM, Loots C, et al. (2011) Esophageal acid exposure decreases intraluminal baseline impedance levels. *Am J Gastroenterol* 106(12): 2093-2097.
13. Blonski W, Hila A, Vela ME, Castell DO (2008) An analysis of distal esophageal impedance in individuals with and without esophageal motility abnormalities. *J Clin Gastroenterol* 42(7): 776-781.
14. Van Rhijn BD, Kessing BF, Smout AJ, Bredenoord AJ (2013) Esophageal baseline impedance values are decreased in patients with eosinophilic esophagitis. *United European Gastroenterol J* 1(4): 242-248.
15. Kessing BF, Bredenoord AJ, Smout A (2011) Erroneous diagnosis of gastroesophageal reflux disease in achalasia. *Clin Gastroenterol Hepatol* 9: 1020-1024.

16. Hemmink GJM, Herrero LA, Bogte A, Bredenoord AJ, Bergman JJ, et al. (2013) Esophageal motility and impedance characteristics in patients with Barrett's esophagus before and after radiofrequency ablation. *European Journal of Gastroenterology & Hepatology* 25: 1024-1032.
17. Agrawal A, Hila A, Tutuian R, Castell DO (2008) Manometry and impedance characteristics of achalasia. Facts and myths. *J Clin Gastroenterol* 42(3): 266-270.
18. Nguyen HN, Domingues GR, Winograd R, Lammert F, Silny J, et al. (2014) Impedance characteristics of esophageal motor function in achalasia. *Dis Esophagus* 17(1): 44-50.
19. Conchillo JM, Selimah M, Bredenoord AJ, Samsom M, Smout AJ (2006) Assessment of oesophageal emptying in achalasia patients by intraluminal impedance monitoring. *Neurogastroenterol Motil* 18(11): 971-977.
20. Tutuian R, Castell DO (2004) Combined multichannel intraluminal impedance and manometry clarifies esophageal function abnormalities: study in 350 patients. *Am J Gastroenterol* 99(6): 1011-1019.
21. Mainie I, Tutuian R, Patel A, Castell DO (2008) Regional esophageal dysfunction in scleroderma and achalasia using multichannel intraluminal impedance and manometry. *Dig Dis Sci* 53(1): 210-216.
22. Spechler SJ, Genta RM, Souza RF (2007) Thoughts on the complex relationship between gastroesophageal reflux disease and eosinophilic esophagitis. *Am J Gastroenterol* 102(6): 1301-1306.
23. Vela MF (2014) Restoring mucosal integrity: "Closing the gap" in the treatment of esophageal eosinophilia. Editorial. *Clin Gastroenterol Hepatol* 12(11): 1830-1831.
24. Rommel N, Tack J, Arts J, Caenepeel P, Bisschops R, et al. (2010) Rumination or belching-regurgitation? Differential diagnosis using oesophageal impedance-manometry. *Neurogastroenterol Motil* 22(4): e97-e104.
25. Kessing BF, Bredenoord AJ, Smout AJPM (2014) Objective manometric criteria for the rumination syndrome. *Am J Gastroenterol* 109(1): 52-59.
26. Barba E, Burri E, Accarino A, Malagelada C, Rodriguez-Urrutia A, et al. (2015) Biofeedback-guided control of abdominothoracic muscular activity reduces regurgitation episodes in patients with rumination. *Clin Gastroenterol Hepatol* 13(1): 100-106.
27. Waško-Czopnik D, Błoński W, Paradowski L (2007) Diagnostic difficulties during combined multichannel intraluminal impedance and pH monitoring in patients with esophagitis or Barrett's esophagus. *Adv Med Sci* 52: 196-198.
28. Martinucci I, de Bortoli N, Savarino E, Piaggi P, Bellini M, et al. (2014) Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. *Neurogastroenterol Motil* 26(4): 546-555.
29. Kohata Y, Fujiwara Y, Yamagami H, Tominaga T, Shiba M, et al. (2015) Usefulness of baseline impedance in patients with proton pump inhibitor-refractory nonerosive reflux disease. *J Gastroenterol Hepatol* 30 (Suppl 1): 36-40.