EDITORIAL

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Impedance – Expected Progress in the Diagnosis of Gastroesophageal Reflux Disease

Impedancja – nadzieje na postęp w diagnostyce choroby refluksowej przełyku

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Abstract

Impedance-pH, a new method for the diagnosis of gastroesophageal reflux disease, is achieving increased popularity and growing acceptance. The principle of the method is measuring the difference in electric potential between two electrodes placed on a catheter and isolated one from another. When the electric circuit is closed by ions from the surroundings, a change in resistance (i.e. impedance) occurs. This method is considered more progressive and accurate than traditional 24-hour intraesophageal pH monitoring and allows distinguishing the character of reflux depending on its chemical composition and consistency. Combining traditional pH monitoring with impedance measurement of the reflux bolus helps in determining the type of symptomatic reflux more precisely, especially when resistance to treatment or extraesophageal complications are found (**Adv Clin Exp Med 2007, 16, 1, 7–12**).

Key words: impedance, intraesophageal pH monitoring, gastroesophageal reflux disease, nonacid reflux.

Streszczenie

Impedancja jest nową metodą diagnostyczną refluksu, która cieszy się rosnącą popularnością i ma coraz większe rzesze zwolenników. Istotą jej działania jest pomiar różnicy potencjałów elektrycznych między dwoma elektrodami umieszczonymi na cewniku i rozdzielonych izolatorem. W czasie zamknięcia obwodu elektrycznego za pomocą jonów z otoczenia dochodzi do zmian oporu (impedancji). Metoda ta jest postrzegana jako nowocześniejsza i dokładniejsza od tradycyjnej pH-metrii 24-godzinnej oraz pozwala na rozróżnienie charakteru refluksu ze względu na jego skład chemiczny i konsystencję. Połączenie tradycyjnej metody pomiaru pH treści zarzucanej z impedancją pozwala z dużo większą precyzją określić typ refluksu powodującego dolegliwości, zwłaszcza przy występowaniu oporności na leczenie lub powikłaniach pozaprzełykowych (**Adv Clin Exp Med 2007, 16, 1, 7–12**).

Słowa kluczowe: impedancja, pH-metria, choroba refluksowa, refluks niekwaśny.

The incidence of gastroesophageal reflux disease (GERD) is continuously growing and encompasses increasingly wider population circles worldwide. It is estimated that GERD is diagnosed in 10% of the world population and that 20% of the population suffers from GERD symptoms at least once a day. Taking into consideration not only the range of the disease, but also its potential complications, both esophageal and extraesophageal, it is imperative to improve knowledge and skills in diagnosing GERD. Intraesophageal 24-hr pH monitoring, which was introduced several years ago, initially fulfilled the expectations of gastroenterologists, in particular in the case of endoscopy-negative reflux disease when the patients complained of typical GERD symptoms and the image of the esophageal mucosa during upper endoscopy was normal. Intraesophegal pH monitoring is still a valuable diagnostic method in questionable cases, when extraesophageal complications are suspected or there is unclear non-cardiac chest pain. This method is also used in partic-

ularly difficult cases resistant to treatment to objectify the progress of treatment and to monitor the efficacy of gastric acid suppression in patients with Barrett's disease. Unfortunately, it is not a perfect method. Although it allows for the detection of the acidic gastric content within the esophagus, its sensitivity is too low, in particular in patients with extraesophageal complications of GERD [1].

Until the present day, most theories concerning reflux episodes and the efficiency of the antireflux barrier in GERD were based on the occurrence of gastroesophageal reflux episodes during intraesophageal pH monitoring. A new diagnostic method appeared in 2002: the measurement of intraluminal impedance (MultiChannel Intraluminal Impedance, or MII), which was developed at the Helmholtz Institute in Aachen, Germany, in the 1990's. It was demonstrated during the development of the impedance measurement that pH monitoring does not detect all reflux episodes, in particular in the case of the absence or low content of acid in the refluxate, even with a very accurate pH interpretation based on additional diagnostic criteria. A meeting of 11 experts on GERD who discussed and critically evaluated the currently available techniques measuring gastroesophageal reflux took place in November 2002 [2].

Multichannel intraluminal impedance is a new technology which allows the detection of bolus movement within the esophagus without the use of radiation or substances marked with an isotope. The basic element of this method is an impedance circuit. There are two electrodes separated by an insulator in a catheter placed within the esophagus. An alternating electric current generator produces a difference in electric potential between the electrodes. The electric circuit can only be closed by ions present within structures surrounding the catheter. When the catheter is surrounded only by air, there is no flow of electric current between the electrodes and the total impedance of the circuit is high. There is a free flow of electric current between the electrodes after placing the catheter into the esophagus because of the electric charges present in the esophageal mucosa, submucosa, and muscularis layer. Likewise, each substance present within the esophagus (saliva, food, refluxate, or gas) causes characteristic changes in impedance. For example, gastric content occurring within the esophagus due to gastroesophageal reflux causes an increase in electrical conductivity and a decrease in impedance due to the high ionic concentration within the refluxate. Every content present within the esophagus causes similar changes in the intensity of the electric current, which enables one to evaluate the character of the esophageal content, differentiating whether it is liquid, gas, or mixed. The MII-pH catheter contains impedance-measuring segments located at 3, 5, 7, and 9 cm (distal esophagus) and at 15 and 17 cm above the lower esophageal sphincter (LES) (proximal esophagus) and antimony pH sensors located at 5 cm above and 10 cm below the LES to allow simultaneous analysis of pH in the distal esophagus and in the stomach. Changes in the impedance progressing from the proximal to the distal esophagus detect antegrade bolus movement due to a swallow, while changes in impedance progressing from the distal to the proximal esophagus followed by a proximal to distal clearance detect retrograde bolus movement due to gastroesophageal reflux [2, 3].

Combined multichannel intraluminal impedance measurement and pH monitoring gives a new method and new quality in diagnosing GERD. The evaluation of esophageal impedance allows for the identification of gastroesophageal reflux and its extent and volume. Simultaneous intraesophageal pH monitoring identifies whether the reflux episode is acidic (pH < 4) or non-acidic (pH > 4). The association between symptom events marked by the patient during an examination and reflux episodes allows for an accurate diagnosis of GERD [4, 5].

Intraesophageal pH monitoring has been considered the gold standard in diagnosing GERD. However, this technique is able to detect only acid reflux, without the possibility of an accurate evaluation of nonacid reflux. It has been suggested that reflux symptoms which persist despite gastric acid suppressive therapy might be caused by nonacidic reflux. New observations performed in patients with symptomatic GERD despite adequate gastric acid suppression have suggested that these symptoms might be caused by nonacidic reflux [6]. It has been demonstrated that during treatment of GERD patients with proton pump inhibitors (PPIs), postprandial reflux becomes predominantly non-acidic [7]. The percentage of acidic reflux episodes decreased significantly, from 45% to 3% ($p = 0.02$), after gastric acid suppressive therapy, whereas the percentage of non-acidic reflux significantly increased, from 55% to 97% ($p = 0.03$) [7]. In addition, the occurrence of symptoms such as heartburn or acidic taste was primarily associated with acid reflux; however, regurgitation was reported with similar frequency during acidic and non-acidic reflux episodes [7].

Taking into consideration the new possibilities arising from the use of impedance-pH, this technique was considered the new gold standard in diagnosing GERD in 2003 based on the results of studies in both children and adults. In combined

impedance-pH, reflux is detected as a change in impedance depending on the type of the bolus moving within the esophagus (retrograde bolus movement). It allows for an evaluation of whether it is acidic or non-acidic based on simultaneous intraesophageal pH monitoring. The detection of non-acidic reflux brings potential advantages to patients with persistent symptoms despite adequate gastric acid suppression [4, 6, 8]. The normal values for 24-hr combined impedance-pH in the absence of gastric acid suppressive therapy were based on the 95th percentile values recorded at 5 cm above the LES in 60 healthy volunteers without GER symptoms who underwent 24-h MII-pH monitoring with impedance measured at six sites (centered at 3, 5, 7, 9, 15, and 17 cm above the LES) and pH 5 cm above the LES. Reflux detected by impedance was characterized by the pH probe as either acidic, weakly acidic, non-acidic, or superimposed acidic reflux. Proximal reflux was defined as reflux that reached the impedance site 15 cm above the LES. The upper limit of normal for the total number of reflux episodes was set as 73 reflux episodes in 24 hours in subjects studied without gastric acid suppressive therapy [9]. Recently, normal values for MII-pH monitoring on gastric acid suppressive therapy were established based on the 95th percentile values recorded at 5 cm above the LES in healthy volunteers, with the normal total number of reflux episodes not exceeding 48 in 24 hours [10]. The additional information provided by simultaneous impedance and pH monitoring has had a major impact on the understanding and clinical management of patients with GERD [11]. Impedance technology caused a redefinition of GERD. Based on the physical refluxate detected by impedance changes, gastroesophageal reflux is classified as liquid, gas, or mixed. On the other hand, based on the chemical properties detected by the pH sensor, gastroesophageal reflux is classified as acidic (pH < 4) or non-acidic (pH > 4). It was observed that the interval when intraesophageal pH is < 4 after a traditional acid reflux episode is a potential "blind spot" during pH monitoring, when the reflux of acidified gastric contents may occur undetected by the pH probe. This has been named "acid rereflux" [12]. It was demonstrated that acid rereflux accounted for 61% of acid reflux episodes during the postprandial period in recumbent patients with severe GERD. Impedance-pH allows for identifying as many reflux episodes as possible, thus providing a more reliable indication of the severity of antireflux barrier incompetence. In addition, it provides more reflux episodes to correlate with patients symptoms, which should improve the sensitivity of the symptom index [2, 10, 12, 13]. This has been shown in 12 patients with GERD.

A recent multicenter study found that 11% of patients presenting with symptoms related to GERD despite gastric acid suppressive therapy had a positive symptom index with acidic reflux, whereas 37% had a positive symptom index with nonacidic reflux [14]. A recent multicenter study in Europe observed that among symptomatic patients receiving PPIs, 33% had a positive symptom index with non-acidic reflux, 5% with acidic reflux, and another 5% with both acidic and non-acidic reflux [15]. The authors also studied patients not receiving PPIs. In that group, among the symptomatic patients 10.8% had a positive symptom index with non-acidic reflux, 32.4% with acidic reflux, and 13% with both acidic and non-acidic reflux [15]. Overall, that study demonstrated that symptoms related to GERD might be associated with non-acidic reflux in patients on and off PPI therapy, mainly regurgitation and cough [15]. Another recent study in Europe evaluating patients off PPI therapy observed that impedance and pH monitoring allowed identifying a higher proportion of patients having positive association with symptoms than pH monitoring alone (77.1% vs. 66.7%, $p < 0.05$) [16].

Reproducibility is an important aspect of every biomedical test. Taking into consideration the use of impedance-pH in diagnosing GERD, the reproducibility of this technique was evaluated in 20 healthy volunteers during 90-min postprandial periods on two separate days [17]. The measured parameters included hourly rates of gas, liquid, and mixed reflux episodes in each recording period, the percentage of time with pH < 4, and the rate of acidic reflux episodes. Based on their results, the authors confirmed the reproducibility of impedance-pH monitoring [17].

The important advantage of impedance-pH over pH monitoring is that combined impedance-pH is able to detect non-acidic reflux. Unlike bilirubin monitoring, impedance-pH does not require the presence of bilirubin in the gastric contents and does not require a special diet during the monitoring. Moreover, the results of the MII-pH are independent of any concomitant motility abnormalities of the stomach. Proton pump inhibitors are efficacious in the majority of GERD patients with erosive esophagitis, and it is believed that non-acidic reflux does not play an important role in these patients. However, non-acidic reflux should be considered in patients with symptoms occurring postprandially or with persistent symptoms despite adequate gastric acid suppression [2]. Identification of the character of reflux episode using MII-pH allows for establishing the reason of

persistent symptoms, in particular during adequate gastric acid suppression. A certain amount of air is transported to the stomach during each swallow. The stomach protects itself against excessive distention by swallowed air through belching (gas reflux). The mechanism of belching (transient lower esophageal sphincter relaxation) is also one of the mechanisms underlying gastroesophageal reflux [18]. MII-pH studies in healthy subjects have shown that though swallowing air promotes belching, in particular in an upright position, it does not facilitate acid reflux, which occurs as a primary event [18, 19]. It has been observed that patients with GERD and healthy controls had similar frequencies of transient lower esophageal sphincter relaxation and reflux of gastric contents. On the other hand, patients with GERD have more acidic reflux and less nonacidic reflux than healthy controls. It has been claimed that differences in the air-liquid composition of the refluxate may contribute to the higher rate of acidic reflux observed in these patients [20].

It is not known why symptoms are caused by only some of reflux episodes. This issue has been investigated using MII-pH performed in 32 patients with symptoms suggestive of GERD after discontinuation of gastric acid suppressive therapy. Symptomatic reflux episodes were associated with a larger pH drop and a higher proximal extent and had a longer volume and acid clearance time compared with asymptomatic reflux episodes. In addition, symptomatic reflux episodes were preceded by a higher esophageal cumulative acid exposure time. Moreover, the proximal extent of reflux episodes preceding regurgitation was greater than those preceding heartburn, and 15% of the symptomatic reflux episodes were nonacidic. It was also observed that symptomatic pure gas reflux was more frequently accompanied by a pH drop than asymptomatic gas reflux. It was suggested that heartburn and regurgitation are more likely to occur when the pH drop is large, proximal extent of the refluxate is high, and volume and acid clearance is delayed. It was also shown that preceding acid exposure causes esophageal sensitization. Furthermore, it was observed that nonacidic reflux is responsible for only a minority of symptoms in patients off gastric acid suppressive therapy. Of note, it was also demonstrated that pure gas reflux associated with a pH drop (“acid vapor”) can be perceived as heartburn and regurgitation [21].

Respiratory symptoms in patients with GERD are often caused by aspiration of refluxed materials into the larynx. However, it was not possible to establish a direct association between these facts before the impedance era. The development of MII-pH has allowed for accurate evaluation of the aforementioned relationship. In order to assess an association between aspiration of refluxed material and airway symptoms, 10 subjects without GERD symptoms or airway disease underwent MII-pH monitoring with a catheter that allowed simultaneous esophageal and pharyngeal monitoring. It was observed that the majority (81%) of the reflux episodes were acidic and reached the mid-esophagus. Reflux episodes into the pharynx were observed more frequently than expected and most of them were nonacidic. Therefore, traditional 24-hour pH monitoring may underestimate the presence of pharyngeal reflux and the combination of impedance with pH monitoring markedly enhanced the ability to accurately detect potential microaspiration leading to extraesophageal manifestations of GERD [22]. Acidic gastroesophageal reflux has been considered one of the most important causes of chronic cough of unexplained origin. Combined MII-pH monitoring with symptom association probability analysis allowed precise determination of the temporal association between cough and gastroesophageal reflux, either acidic or nonacidic, and identification of a subgroup of patients with chronic cough clearly associated with nonacidic reflux [23]. It was recently reported that the fundoplication due to chronic cough occurring in patients on gastric acid suppressive therapy and associated with nonacidic reflux during MII-pH may cause significant symptomatic improvement [24]. Another recent study demonstrated that among 50 patients with persistent cough despite gastric acid suppressive therapy, 26% had a positive symptom index with nonacidic reflux [25]. This study also showed that a positive symptom index for nonacidic reflux may be helpful in selecting patients who benefit from antireflux surgery [25]. In that study, six patients with a positive association of cough with nonacidic reflux became asymptomatic after Nissen fundoplication and stopped taking their acid suppressive medications during a median time follow-up of 17 months [25].

Barret’s esophagus is one of the distant complications of GERD. It is caused by many years of esophageal exposure to gastroesophageal reflux. However, in the light of MII-pH findings we should ask the question whether it is caused only by acidic reflux. The treatment of patients with Barrett’s esophagus is still controversial. Patients with Barret’s esophagus should undergo endoscopic surveillance and continuously use a high dose of proton pump inhibitors; however, there is debate concerning its dosing. Traditional pH monitoring has allowed so far to establish the lowest efficacious dose of proton pump inhibitor, but this strategy has

not always been sufficient. MII-pH is a potential tool which may allow establishing the highest dose of proton pump inhibitor causing maximal gastric acid suppression. By excluding reflux types other than acidic, this method may allow for accurate and efficacious dosing of the appropriate therapy [26].

Despite its many advantages, impedance has also its limitations. Above all, the interpretation of an MII-pH tracing requires some experience: sometimes distinguishing between reflux episodes and impedance changes due to a swallow or detecting rereflux or reflux occurring within the short segment of the esophagus might be difficult. Although the interpretation of an MII-pH tracing is a rather tedious job requiring a lot of patience, it is worth doing due to the new possibilities in diagnosing GERD and the advantages for patients.

The introduction of every new diagnostic method gives new hopes. Will impedance fulfill these hopes? Results of more and more numerous studies will stabilize the role of this methodology in the diagnosis of the GERD.

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